CONTROL OF ACID-BASE STABILITY IN THE NEWLY BORN *

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THE object of the present exercise (in the jargon of the day) is to discuss the regulation of acid-base stability in newborn animals, but the fœtus must have a word or two first. It is now becoming clear that the fœtus does not depend for its wellbeing upon the workings of a placenta which is governed solely by the laws of diffusion, but it regulates both the volume and composition of its own internal environment from the day it is conceived. The ways and means by which it does this and how it deals with its H-ion regulations are by no means understood as yet, but a few facts are known and they will no doubt fall into their proper place in the jigsaw puzzle when it is finally solved.

Some animals, such as the pig, have a large allantoic sac into which the products of the mesonephros and later of the metanephros are passed. In the pig the fluid in this sac has a very low concentration of sodium and chloride; it is very hypotonic relative to plasma and it has a pH of about 6, largely due to carbonic acid. We have evidence that the mesonephros does not elaborate such a fluid (Stanier 1960) and that the change in composition is brought about by the chorioallantoic membrane (Widdowson and McCance 1958, Crawford and McCance 1960), but the metanephros in the pig and certainly also in man is capable of producing a strongly hypotonic acid urine and does so to a greater or lesser extent throughout the latter half of pregnancy. The newborn animal, therefore, does not enter the world with a kidney which has never played any functional part in acid-base control, although how this control is shared out between the chorioallantoic and amniotic membranes, the placenta, and the kidney remains to be discovered.

Adults

The kidney of an adult does not as a rule secrete a urine with a pH much below 4·8. One-tenth of a milliequivalent of hydrochloric acid would lower the pH of a litre of distilled water well below this, yet the two kidneys of an adult normally excrete upwards of 70 mEq. of H ions per day and can excrete far more should the need arise. They are able to do this:

(*a*) By lowering the pH of the urine to the limits imposed upon them by nature.

(*b*) By virtue of the fact that there are buffer substances in the urine which maintain the pH above 4·8 even when large amounts of H ions are secreted into it. The most important buffer substances in mammalian urine are the phosphates; creatinine and the organic acids come very poor seconds, and a urine without phosphates in it is very limited in its capacity to carry free hydrogen ions within the prescribed limits of pH.

(*c*) By combining H ions with NH_3 to form ammonium ions. These have the same physiological significance as H ions because their production enables the kidney to excrete sulphates, chlorides, and similar acid radicles within the pH limitations of the kidney yet without at the same time having to excrete sodium or potassium salts. The usual diet of a person in Western Europe or the United States leads to the formation of a urine with a pH of about 6. Nearly half of the ions excreted are likely to be in the form of titratable acid and 50–60% in the form of ammonium salts.

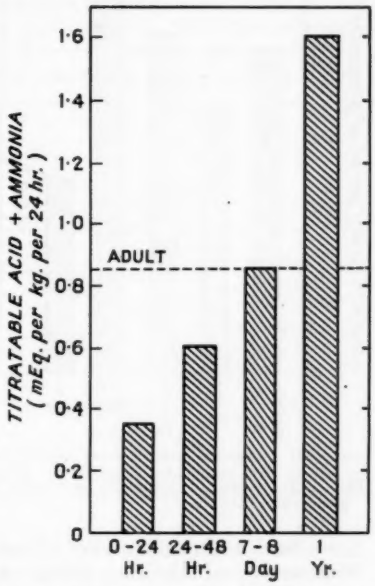

Fig. 1—Excretion of titratable acid and ammonia by infants of various ages and by adults.

The First Days of Life

The urine produced by a healthy fœtus in the last days of gestation usually has a pH of about 6 (McCance and Widdowson 1953), and this is true also of the newborn baby (Weber 1960), but before birth (always) and after birth (if breast-fed) the urine of a thriving baby contains practically no phosphates. In consequence there is a very definite limitation on the amount of free H ions which can be excreted in the urine, and a tendency for most of them

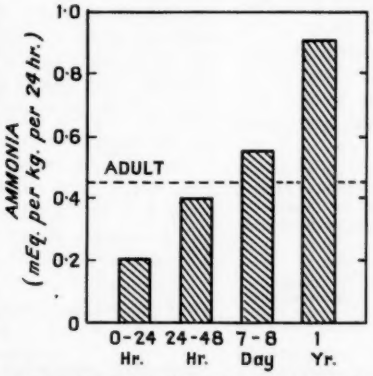

Fig. 2—Excretion of ammonia by infants and by adults.

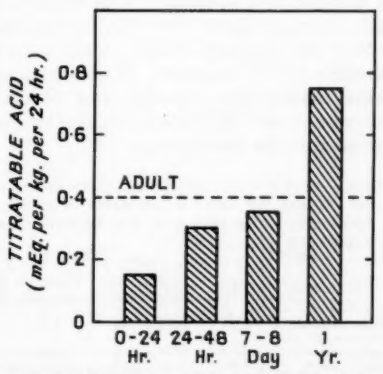

Fig. 3—Excretion of titratable acid by infants and by adults.

* Based on a Litchfield lecture delivered at the University of Oxford on May 11, 1960.

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to leave the kidney as ammonium salts (McCance and von Finck 1947). In the first two days after birth much less titratable acid and ammonia is excreted by the newborn than by the adult per kilogramme of bodyweight, but by the seventh day on breast milk the amounts are about the same. This "build-up" is shown somewhat diagrammatically in fig. 1, and the way in which the infant differs from the adult in the pattern of its excretion of ammonia and titratable acid in figs. 2 and 3. Without stating the ages of his "newborn" subjects Weber (1960) gives a figure for their titratable acid of 0·3 mEq. per kg. per day. Widdowson and McCance (1958) obtained about this amount for breast-fed babies at seven days. Had these results been expressed p:r unit of surface-area (see later) the infants would have made a much worse showing, and it is not certain which method of comparison should be used. Fig. 4, however, shows that the newborn infant actually produces more ammonia per unit of glomerular filtrate than adults do, and this is a valuable "internal" comparison about which there can be no controversy.

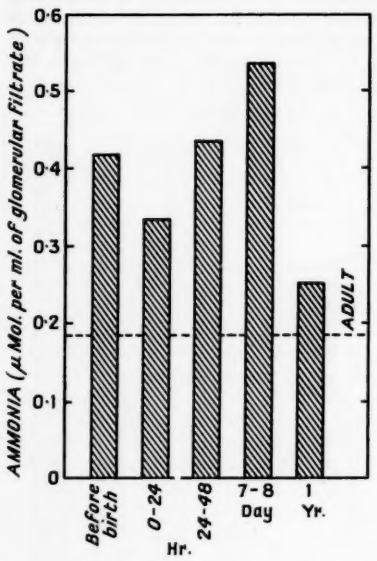

Fig. 4—Excretion of ammonia per unit of glomerular filtrate.

It has been recognised for many years that infants have somewhat lower plasma bicarbonates and pH than adults (Marples and Lippard 1932). This is a "steady state" in thriving infants, but it resembles the similar but pathological steady state of a mild but untreated case of renal acidosis. Latner and Burnard (1950) first showed that the administration of neutral phosphates to such a patient led to the excretion of more H ions in the form of titratable acid. Table I shows that this has also been found to be true of the newborn infant. Only a very small average decrease in the excretion of ammonia was recorded in these experiments (Hatemi and McCance 1960); the decrease is not significant, but similar results have been obtained in the newborn pig.

TABLE I—EFFECT OF GIVING 120 mg. P PER DAY IN SOLUTION AT pH 7·4 ON URINARY pH AND ON THE RATES OF EXCRETION OF INORGANIC PHOSPHATE, TITRATABLE ACID, AND AMMONIA IN BREAST-FED INFANTS 7 DAYS OLD

Treatment	pH	Phosphate (μEq./kg./hr.)	Titratable acid (μEq./kg./hr.)	Ammonia (μEq./kg./hr.)
Breast milk alone*	6·2	0·75±0·46	6·3± 4·7	23·5±6·2
Breast milk plus phosphate ..	6·35	56·9±12·4	22·0±11·4	21·5±4·9
Cow's milk* ..	5·9	93·0±23·2	42·0±10·8	30·0±5·4

* Data from McCance and Widdowson (1960).

The Effect of Acidifying Drugs

Although thriving infants are able to maintain a satisfactory acid-base balance, they are liable to develop a much more serious acidosis than adults under quite a mild stress, and the well-known effects of "protein" milk are a good illustration of this (Darrow et al. 1945, Hoffman et al. 1948). Why human infants should be so liable to acidosis has never been exactly defined, largely because the matter has never been carefully investigated. The experiments of Gordon et al. (1948) and Fomon et al. (1959) were limited in scope and not planned with this object in mind. Table II shows the total CO_2 and the chlorides in the serum before and after giving 54 mEq. per sq. m. of ammonium or calcium chloride in a single dose to breast-fed infants seven days old and to adults. Initially, as others have found, the infants showed signs of a very mild acidosis. The drugs produced changes of a somewhat greater degree in infants and the stimulus to excrete the chloride ions and the H ions should have been at least as great, if not greater. Fig. 5 shows the effect on the average pH of the urine. The response of the adults was characteristic; that of the infants differed in two respects (1) the pH fell less rapidly and (2) it did not fall so far. Had further doses of NH_4Cl been administered it is probable that the plasma-bicarbonate would have gone on falling and that the average pH of the urine would have reached 4·9 within a day or so; this is what Gordon et al. (1948) found in serum and in twenty-four-hour specimens of urine after giving ammonium chloride to "older", even if "premature", babies in divided doses for several days. Nevertheless fig. 5 shows that the initial response of the infants was notably weaker than that of the adults to a similar stimulus.

TABLE II—EFFECT OF GIVING 54 mEq. per sq. m. OF AMMONIUM CHLORIDE OR CALCIUM CHLORIDE ON THE CHLORIDE AND BICARBONATE IN THE PLASMA OF ADULTS AND OF BREAST-FED INFANTS 7 DAYS OLD WITH AND WITHOUT PRETREATMENT WITH NEUTRAL PHOSPHATE

Subjects	Chloride (mEq./l.)		Bicarbonate (mEq./l.)	
	Before	After	Before	After
Adults	106±2·0	109±2·3	29±1·6	26±2·2
Infants on breast milk alone	109±3·2	113±4·1	24±2·1	19±3·3
Infants on breast milk plus phosphate	109±3·3	114±2·8	25±1·4	21±2·5

Fig. 6 shows the effect of the acidifying drugs on the excretion of free H ions. The adults made a large and rapid response. This was due partly to the speed with which the pH of the urine fell and partly to the amount of phosphates excreted; this was considerable at the beginning and increased later owing to the time of day at which the experiments were done and to the normal diurnal rhythm. The infants were excreting very little phosphate

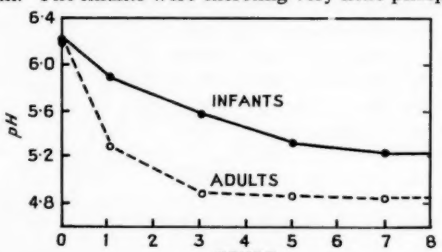

Fig. 5—pH of urine before and after giving 54 mEq. of ammonium chloride or calcium chloride per square metre to adults and to breast-fed infants 7 days old.

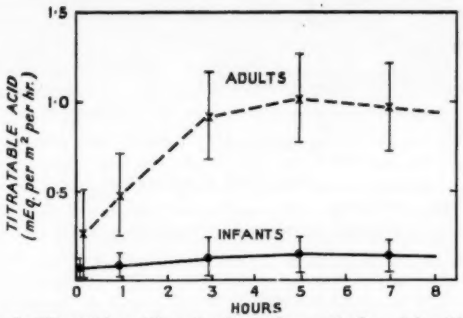

Fig. 6—Titratable acidity of urine before and after giving 54 mEq. of ammonium chloride or calcium chloride per square metre to adults and to breast-fed infants 7 days old.

and their response was inevitably limited by this, but more free H ions would have been excreted if the pH of their urine had fallen more rapidly. Fig. 7 shows the effect of the ammonium and calcium chlorides on the excretion of H ions as NH_4 salts. The first point here is the comparatively large initial output in infancy which might have been anticipated from figs. 2 and 4, but which would not have been predicted from the work done in vitro (Robinson 1954, Hines and McCance 1954). The second point is that after the ammonium chloride the infants did not, like the adults, excrete much more ammonia than before. They were nevertheless excreting as much as the adults per unit of body-weight, and Ruben et al (1956) obtained a similar

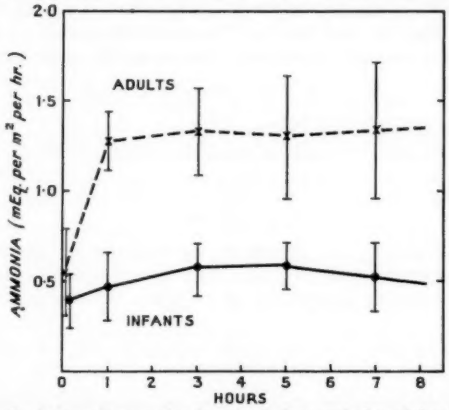

Fig. 7—Ammonia excretion in urine before and after giving 54 mEq. of ammonium chloride or calcium chloride per square metre to adults and to breast-fed infants 7 days old.

result after giving 10 mEq. per kg. of ammonium chloride for nine days to premature infants twenty-eight days old. All this looks as though the amounts of ammonia being excreted at seven days were already considerable and that the kidney was working in this respect almost to the limits of its capacity. It was, nevertheless, producing much less ammonia than that of an adult per square metre of body surface; and the work of Fomon et al. (1959) and of Ryberg (1948) indicates that, although these infants might have increased their production of ammonia if the acidosis had been prolonged, adults would have increased their production still more, and consequently the discrepancy between the two age periods would have increased.

The Effect of Phosphates

The next step was to repeat these experiments after giving both the infants and the adults a solution of neutral phosphates in divided doses. This greatly multiplies the comparisons that can be made. Fig. 8 shows that the urines passed by the infants given neutral phosphates were slightly less acid both before and after ammonium chloride had been given than the urines of the other infants. In spite of this, as fig. 9 shows, the presence of phosphates in the urine enabled the infants to raise the excretion of titratable acids to quite a high level after the ammonium chloride had been given. Similar observations have been made on premature infants by Ruben et al. (1956) and on acidotic dogs (Pitts and Lotspeich 1946) perfused with neutral phosphate. In keeping with the higher values for pH in the urine fig. 10 shows that the excretion of H ions

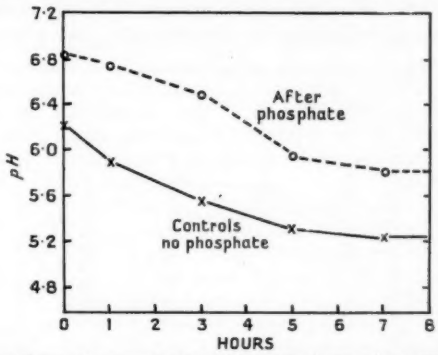

Fig. 8—Effect of pretreatment with neutral phosphate (120 mg. phosphorus per day) on pH of urine before and after giving 54 mEq. of ammonium chloride per square metre to breast-fed infants 7 days old.

as ammonium salts was, if anything, *lower* after the phosphates had been given, and a similar effect can be observed in table I, although in neither case were the differences significant. Ammonia excretion, however, tended to fall towards the end of the experiment when the excretion of free H ions was going up (fig. 9). This threefold effect of giving phosphates suggests that, although the absence of phosphates from the urine was certainly limiting the output of titratable acid, the overall capacity to produce and excrete H ions in any form was also curtailing the infants' response to ammonium chloride. This can be expressed in another way by saying that after this large dose of ammonium chloride neither the available titratable acidity nor the capacity to produce NH_3 were being fully exploited to correct the acidosis.

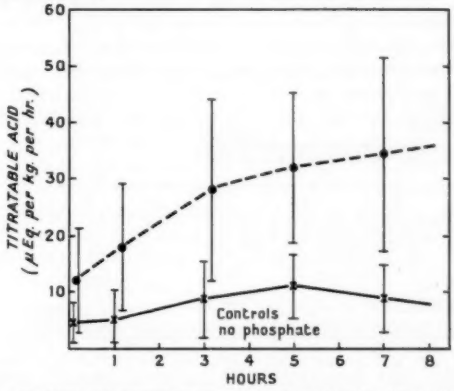

Fig. 9—Effect of pretreatment with neutral phosphate (120 mg. phosphorus per day) on excretion of titratable acid after giving 54 mEq. of ammonium chloride per square metre to breast-fed infants 7 days old.

Schiess et al. (1948) showed that the administration of neutral phosphates to three men with an ammonium-chloride acidosis increased the excretion of titratable acid. Similar results were obtained in the present investigation of healthy men and women. Since, moreover, the pH of the urine fell to almost the same level and the excretion of ammonia was not reduced by the administration of phosphates, the overall output of H ions was considerably increased, and these findings indicate that in adults the production of H ions at the appropriate part of the tubules was not limiting the rate of excretion of the acid load.

Further Comparisons with Adults

Fig. 11 shows the maximum rate of H-ion excretion attained by the infants and the adults after the administration of phosphates, and the difference between the two is very evident. It also shows the greatest H-ion "clearances" attained. The H-ion clearance is a method of expressing a person's ability to eliminate H ions, worked out by Elkinton and McCance when the former was visiting Cambridge in 1958 (Elkinton, Huth, Webster, and McCance 1960). It is a very sensitive index of a person's capacity to do this because it takes into account not only the quantity excreted per unit of time but also the level of plasma-CO_2 at which this rate of excretion is achieved. It probably demonstrates the true relationship of the newly born to the adult in this respect better than anything else.

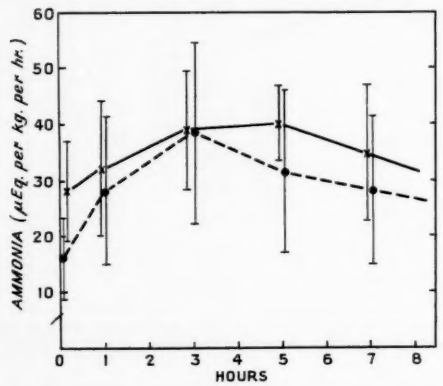

Fig. 10—Effect of pretreatment with neutral phosphate (120 mg. phosphorus per day) on ammonia excretion after giving 54 mEq. of ammonium chloride per square metre to breast-fed infants 7 days old.

There are two other ways in which the ability of the newly born to correct an acidosis may be summarised and compared with that of an adult. The first (shown in fig. 12) is to compare the percentage of the dose of potential H ions administered which were excreted within eight hours. The infants excreted a mere 3–4%; and, although phosphates raised the figure to nearly 9%, they improved the rate of excretion in adults by a greater percentage than this for the reasons already given. The second way (shown in fig. 13) is to compare the percentage of the chloride part of the ammonium chloride excreted within eight hours. Much more of the chloride ions than the H ions are always excreted in the first few hours, but again the infants made a much poorer showing. When phosphates were being administered less chloride was excreted. The phosphates replaced the chlorides in the urine. This was due to the following reason. Giving the phosphates did not increase the excretion of fixed base and other cations so much as it increased the excretion of phosphates. There was no compensatory fall in the output of undetermined anions, and consequently the output of chlorides had to fall. Rapoport and West (1950) also obtained a fall in the excretion of chloride when they administered anions with a preferential rate of excretion.

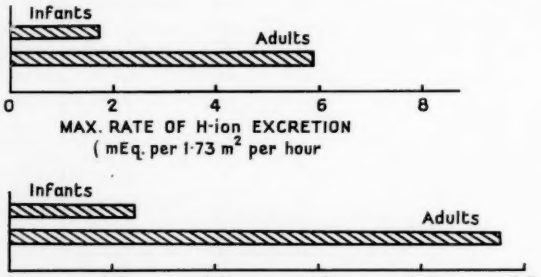
Infants
Adults
0 2 4 6 8
MAX. RATE OF H-ion EXCRETION
(mEq. per 1·73 m² per hour
Infants
Adults
0 0·5 1·0 1·5 2·0 2·5
MAX. CLEARANCE INDEX (per 1·73 m²) for H-ions

Fig. 11—Maximum rate of H-ion excretion and maximum clearance indices for H ions after administration of phosphate.

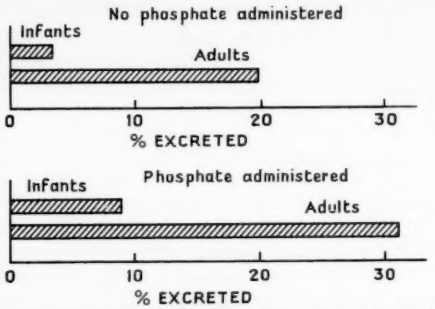

Fig. 12—Percentage of H ions (generated from ammonium chloride) excreted by infants and adults within 8 hours.

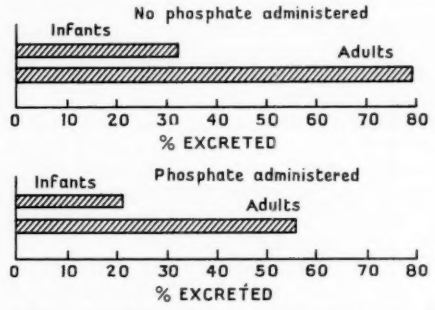

Fig. 13—Percentage of chloride ions (in ammonium chloride) excreted by infants and adults within 8 hours.

Conclusions

So far this lecture has been rather a dismal catalogue of newborn inefficiency—yet acid-base stability is normally maintained. As with many other aspects of somatic stability in the newly born it is achieved by a process of integration between food, growth, and renal function. Growth helps by leading to the incorporation of many of the "sulphur" aminoacids in the diet into body proteins and mucopolysaccharides. Food is also important, and the infant cannot tolerate any regime which has not been planned to allow for its limitations. The effects of protein milk have already been mentioned. Cow's milk in itself is interesting in this respect. It contains many more

sulphur-containing aminoacids, and thus raises considerably the amount of acid products of metabolism requiring excretion. It also, however, contains more phosphates. These are absorbed with fixed base and can be excreted in combination with H ions, thus increasing the means at the disposal of the kidney for maintaining the acid-base balance. By means such as these the infant is able to maintain reasonably good acid-base stability. The low plasma-bicarbonate levels, however, vis-à-vis those of an adult, indicate that even on mother's milk stability is not achieved at levels which are physiologically desirable in adults. This raises an important general principle which applies to the maintenance of most of the great steady states in the newly born. At all ages a departure from the normal constitutes a stimulus to correct it, and until the mechanisms break down the further the departure from the normal has become the greater the response made to correct it. In adults a very small stimulus can be remarkably effective, but in the newly born a greater departure from the normal is usually required to elicit the same "corrective" response.

The level of plasma-CO_2 found in adults is sufficiently on the acid side of physiological neutrality to activate the kidneys into excreting the acid products of metabolism generated every day. In the newly born, however, the level of plasma-CO_2 only becomes capable of inducing the excretion of the daily production of acid when it has fallen further from the physiological neutral point. It is to be noted, moreover, that smaller amounts of these acids are produced by the infants per unit of surface-area. The kidney of the patient with renal acidosis or chronic nephritis requires the "assistance" or the "stimulus" of a still greater internal acidosis.

In conclusion, therefore, one may say that the kidneys of the breast-fed newly born are demonstrably underdeveloped in their ability to establish the adult pH gradients between blood and urine, and to excrete H ions into the urine, and are further handicapped by the absence of buffer substances there. Nevertheless, internal stability is normally achieved and maintained since the food is so designed that it gives rise to very few acid products of metabolism. Even on this perfect diet, however, the level of plasma-CO_2 at which equilibrium is attained is lower—i.e., further from the physiological neutral point—than it is in adults.

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GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

A New Ætiological Factor of Severe Neonatal Jaundice

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IN West European and North American communities rhesus hæmolytic disease of the newborn was the commonest cause of kernicterus before the introduction of exchange transfusion, and it remains today the main indication for this method of treatment. ABO hæmolytic disease and prematurity are also common causes of severe jaundice in the newborn.

In other communities the ætiological distribution of severe neonatal jaundice is different (Sutow et al. 1956, Boon 1957, Shnier and Levin 1959), and this seems to apply to Greece. Thus from Jan. 1, 1957, to June 30, 1960, 220 babies, either born in the Alexandra State and University Maternity Hospital (total number of live births during this period 24,239) or admitted to the neonatal unit of this hospital, received one or more exchange transfusions on account of severe neonatal jaundice. Moreover during the same period 30 infants were admitted with established kernicterus. The ætiological distribution of the severe neonatal jaundice in these cases is shown in table I.

TABLE I—ÆTIOLOGY OF SEVERE ICTERUS IN INFANTS WHO RECEIVED EXCHANGE TRANSFUSION OR HAD KERNICTERUS ON ADMISSION

—	Exchange-transfusion cases		Kernicterus cases	
	Full term	Prematures	Full term	Prematures
Hæmolytic disease due to Rh incompatibility ..	41	0	0	0
ABO incompatibility	54 (*48*)	20 (*10*)	4 (*2*)	1
No incompatibility ..	59	46	23	2
Total	154	66	27	3

Figures in parentheses refer to number of infants who in addition to blood-group incompatibility had early appearance of the jaundice.

Of the 22,351 full-term babies born in the Alexandra Maternity Hospital, 101 (0·45%) required exchange transfusion. In this group rhesus hæmolytic disease of the newborn severe enough to necessitate exchange transfusion was encountered in 23 newborns—a frequency of 1:1000. 35 infants (0·15%) required an exchange transfusion in the absence of any incompatibility.

The group of 82 full-term infants with no incompatibility (table I) comprised 50 males and 32 females. 40 were first-born, while in the 42 families with a previously live-born infant there were 11 siblings affected with severe neonatal jaundice.

Although it is not always easy to obtain conclusive evidence of increased hæmolysis in the neonatal period, we could say with reasonable certainty, on the basis of the course of hæmoglobin and bilirubin values, that increased hæmolysis was present in 58 of the 82 infants. Moreover this increased hæmolysis was certainly of postnatal origin. In some babies the hæmolysis started early, as the early

appearance of the jaundice and the rapid rise of serum-bilirubin values showed. In others it began on about the third to fifth day, this later onset not denoting a milder course. In some cases kernicterus did not appear till the tenth day. Of the 82 babies 15 had received a small dose (1–5 mg.) of a Vitamin-K analogue after the appearance of the jaundice. 12 of these were among the group who were admitted with kernicterus. In the babies treated with exchange transfusion the hæmolytic process seemed to stop and the serum-bilirubin, after a temporary rise which sometimes necessitated a second exchange transfusion, started to fall, the jaundice disappearing completely in a few days. In the babies who, owing to established kernicterus, did not receive an exchange transfusion and survived, the hyperbilirubinæmia followed a similar but more protracted course. In many of these babies high values of conjugated bilirubin were found after the first few days, pointing to an active enzyme system of bilirubin conjugation.

This group of infants with severe neonatal jaundice, although formed originally by negative criteria—namely, the absence of incompatibility and prematurity—presented enough common features to suggest a common cause, probably hæmolytic and genetically determined. Of course, the transient immaturity of the liver-enzyme system which forms the common background of all non-obstructive types of neonatal jaundice must have been also present.

In our search for an inherited hæmolytic factor we could exclude the various hæmoglobinopathies prevalent in the Mediterranean area. In the past few years a new familial abnormality of the red blood-cells has been described (Dern et al. 1954). This abnormality, which is the basis of hæmolysis caused by primaquine and many other drugs, has been shown to be linked to a deficiency of an enzyme of the erythrocytes—the glucose-6-phosphate dehydrogenase (G.-6-P.D.) (Carson et al. 1956). An inherited deficiency of the same enzyme was also found in patients with favism (Sansone and Segni 1956, Szeinberg et al. 1957, Larizza et al. 1958).

The mode of transmission of this genetic defect is probably sex-linked, the responsible gene being located on the X chromosome. Accordingly males inheriting the abnormal gene from their mothers show absence of the enzyme. Females may inherit it from either parent or from both; therefore there may be homozygous normal, heterozygous, or homozygous abnormal. The heterozygous female may show a variable degree of enzyme deficiency.

Since favism is common in the Greek race, study of the G.-6-P.D. in the babies with unexplained hæmolytic neonatal jaundice and in their families was warranted.

Method

Of the methods available for the estimation of the G.-6-P.D. activity of the red cells, we chose the one of Motulsky and Campbell (1960). By this procedure the enzyme activity is assayed using the dye brilliant cresyl-blue as an indicator. Although by this method an exact quantitation of the enzyme is not possible, it has the great advantage that it is simple and rapid.

Oxalated blood was used in the majority of instances, but occasionally blood collected in anticoagulant acid-citrate-dextrose solution or heparin was also used. The samples were kept in the refrigerator until tested, usually within a week. In order to minimise possible variation due to different hæmoglobin concentration, packed red cells rather than whole blood were used for the test.

The procedure is briefly as follows: 0·01 ml. of packed red cells is added to 1·0 ml. of distilled water and 0·2 ml. of tris-buffer, 0·74 *M*, pH 8·5. To this are added in succession:

0·05 ml. of a solution of 0·165 g. glucose-6-phosphate, disodium salt, in 10 ml. H_2O ('Sigma').

0·05 ml. of a solution of triphosphopyridine nucleotide 0·1% (British Drug Houses).

0·25 ml. of a solution of 0·32 g. brilliant cresyl-blue in 1000 ml. H_2O (National Aniline).

After good mixing the reagents were overlayered with mineral oil. The tubes were then incubated in a water bath at 37°C and inspected for decolorisation against daylight at 50, 75, 100, 120, 180 minutes, and 6 hours.

All samples of blood where decolorisation was complete at 100 minutes were considered as exhibiting normal G.-6-P.D. activity (non-reactors). All samples, either from cord blood or from adults, which were not decolorised at all up to 3 or 6 hours were considered as having practically no enzyme activity (reactors). Partial decolorisation at 100 minutes was taken as a sign of partial enzyme deficiency (intermediate reactors). All samples which did not react normally were tested again at least once on the same specimen and a third time on a new sample, whenever available. No difficulty was encountered in interpreting the results on complete reactors; but decolorisation of intermediate degree was not always easy to assess. This is to be expected with a basically qualitative method. Nevertheless, for the purposes of the present investigation this method was considered satisfactory.

Material

In order to investigate a possible connection between lack of G.-6-P.D. of the erythrocytes and development of neonatal jaundice we tried to establish the incidence of this defect on the one hand among the group of infants with otherwise unexplained neonatal jaundice and on the other hand in a group of infants which can be broadly defined as controls. In view of the known hereditary character of the defect the parents and relatives of these babies were also studied.

The material of the present study consists of the following groups:

Group 1.—100 newborn infants born in our hospital collected at random (cord blood).

Group 2.—All infants, either born in our hospital or sent to us from outside, who developed neonatal jaundice severe enough to necessitate a serum-bilirubin estimation, and their parents. These cases were consecutive over a period of six months and were therefore unselected.

Group 3.—Surviving members of families with a history of severe unexplained neonatal jaundice. Most of these families had come to our notice before we started testing for enzyme deficiency and were selected from our past material either because of easy accessibility or because it was evident from our records that the jaundice of the affected infants was due to excessive hæmolysis. A few families came to our notice when the mother was delivered in our hospital and gave a history of a previous infant exhibiting severe neonatal jaundice.

Results

The results of our search for G.-6-P.D. activity of the erythrocytes are shown in tables II–IV.

Group 1: random cord samples (table II).—Only 1 of the 100 infants tested had a G.-6-P.D. deficiency. None exhibited severe enough jaundice to necessitate serum-bilirubin estimation.

Group 2: current cases of neonatal jaundice (table III).—This group was subdivided according to the likely ætiology of the jaundice. In the subgroup of rhesus hæmolytic disease of the newborn where the ætiology of the jaundice was certain, no infant or parent with enzyme deficiency was found. In the subgroup with ABO incompatibility this was taken prima facie as the cause of the jaundice, but other factors could not be excluded. In this subgroup 2 male infants were reactors and their mothers intermediate reactors. 1 of them had kernicterus by the time of his admission, and the serum-bilirubin of the other

TABLE II—G.-6-P.D. ACTIVITY IN RANDOM CORD SAMPLES

—	Tested	Reactors*
Male	56	1
Female	44	..
Total	100	1

* Reactors = G.-6-P.D.-deficient

did not reach critical levels. Another mother was an intermediate reactor, but her male infant was a non-reactor. The father of a non-reactor male infant was a reactor. Obviously in the last 2 cases the enzyme defect in the parents was a chance finding unconnected with the jaundice of the infants. In the subgroup of jaundice in premature infants, liver immaturity was regarded as the main ætiological factor, but again others could not be excluded. 1 male infant was found to be a reactor and his mother intermediate. We included in our tests a number of jaundiced full-term newborns in whom there was no incompatibility and the serum-bilirubin never exceeded 15 mg. per 100 ml. This subgroup was loosely called "physiological jaundice"; there were no cases of G.-6-P.D. deficiency among the infants, and the father of only 1 male infant was a reactor.

In the subgroup of infants with severe jaundice of unknown cause there were 10 male reactors; of these, 5 had kernicterus by the time of their admission and 1 had

TABLE III—G.-6-P.D. ACTIVITY IN CURRENT CASES OF NEONATAL JAUNDICE

Ætiology of Jaundice	Sex of Infants	Infants		Mothers		Fathers	
		Tested	Reactors†	Tested	Intermediate reactors†	Tested	Reactors†
Known:							
Rhesus H.D.N.*	M	10	..	6	..	4	..
	F	5	..	5	..	5	..
ABO H.D.N.*	M	10	2	9	3	9	1
	F	14	..	11	..	10	..
Prematurity	M	16	1	10	1	8	..
	F	4	..	2	..	2	1
"Physiological" jaundice	M	7	..	4	..	3	1
	F	5	..	5	..	3	..
Total		71	3	52	4	44	3
Unknown:	M	13	10	13	2	13	..
	F	4	..	4	..	4	3
Total		17	10	17	2	17	3

* H.D.N. = hæmolytic disease of the newborn.
† Reactors = G.-6-P.D.-deficient

doubtful signs and was therefore treated with exchange transfusion. Of these 6 infants, 3 received a vitamin-K analogue prior to development of kernicterus but after onset of jaundice, 1 was exposed to naphthalene inhalation, and in the other 2 no extrinsic precipitating factor was found. Of these infants 1 died subsequently following a hæmolytic episode caused by an injection of a pyrazolone derivative. 3 infants received an exchange transfusion and recovered. 1 of these infants (see figure, family 1) had been given an injection of vitamin-K analogue, and in the other 2 there was no extrinsic factor. Lastly, 1 infant did not require any treatment. In 3 infants the enzyme was normal in them and their parents. All received an exchange transfusion and recovered; definite signs of hæmolysis were present in 1 of them.

Among the 4 females with severe jaundice of unknown cause no enzyme defect could be detected, but the fathers

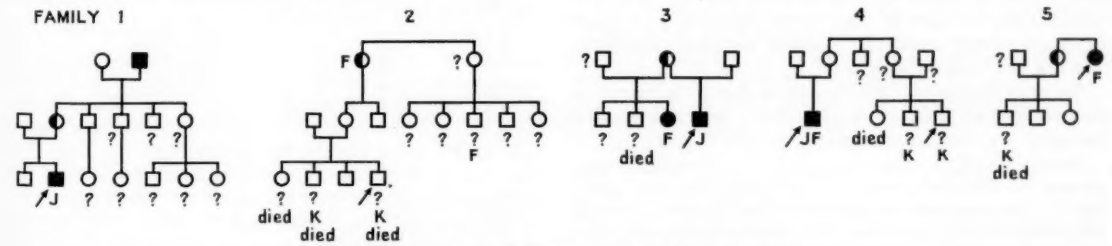
TABLE IV—G.-6-P.D. ACTIVITY IN FAMILIES WITH HISTORY OF SEVERE NEONATAL JAUNDICE OF NO KNOWN CAUSE

Group	Sex of Infants	Infants		Mothers		Fathers	
		Tested	Reactors*	Tested	Intermediate reactors*	Tested	Reactors*
Affected infants tested	M	11	9	10	3	10	1
	F	2	1	2	..	1	1
Affected infants not tested	M	8		6	3	4	1
	F	3		3	..	3	2

* Reactors = G.-6-P.D.-deficient.

of 3 were reactors and the infants therefore heterozygous. 1 of them was exposed to naphthalene inhalation after birth and died with kernicterus. The other received vitamin-K analogue parenterally shortly before admission. Despite a serum-bilirubin value of 43·2 mg. per 100 ml. no signs of damage to the central nervous system were found, and the infant recovered after exchange transfusion. The 3rd also recovered after exchange transfusion. The remaining female was a typical infant of a prediabetic mother. The infant and the parents were non-reactors.

Group 3: families with history of severe neonatal jaundice of unknown cause (*table IV*).—As could be expected from the method of selection, a very high proportion of the infants and their parents showed enzyme deficiency. In the subgroup of affected infants tested for enzyme defect there were 9 male reactors and, of these, 5 had kernicterus and 4 recovered after exchange transfusion. 1 of those who had kernicterus and 1 of those who recovered are brothers. In another family a female had died from kernicterus while a male sibling who was found to be a reactor has survived with neurological sequelæ. In this family the father was found to be a reactor while the mother appeared normal but was probably heterozygous in view of a male reactor child. In this family, however, as in one mentioned later, a different mode of inheritance cannot be excluded. Another infant survived after exchange transfusion early in 1956, and four years later he was seen with favism; 2 male first cousins from the maternal side had severe neonatal jaundice and both survived with neurological sequelæ (see figure, family 4). The half-sister of another male infant was seen with favism (figure, family 3).



Families with clinical manifestations of G.-6-P.D. deficiency.

Closed circles or squares = reactors; half-closed circles or squares = intermediate reactors; open circles = non-reactors; ? = not tested; J = severe neonatal jaundice; K = kernicterus; F = favism.

Of the two male non-reactors 1 had recovered after exchange transfusion from an attack of naphthalene-induced hæmolysis and the other recovered after exchange transfusion; a previous male sibling of the latter had died from kernicterus. Both infants' parents were non-reactors. The 2 females of this subgroup survived with kernicterus; 1 was found to be a reactor, the other a non-reactor. Nevertheless in her family a previous female sibling had died with kernicterus, and her father was a reactor while the mother and a younger brother were normal.

In the subgroup of affected infants not tested 7 male infants died with kernicterus, 4 belonging to two families (see figure, family 2, for the first family). In the other family the mother was found to be normal but the father and a younger female infant were reactors. In all probability the mother also must have been heterozygous. 2 more mothers with infants who died from kernicterus were found to be intermediate reactors, and also the mother of an infant that survived after exchange transfusion. The sister of one of these mothers suffered from favism and is a reactor (figure, family 5). Of the 3 females, in 2 the fathers were found to be reactors, and both infants died from kernicterus; the other, whose parents are non-reactors, survived after exchange transfusion but was not tested.

In 34 families in which at least one member was found to have G.-6-P.D. deficiency there were 54 male and 20 female children. Of the 54 male children 37 were tested and 24 were reactors. Of the 24 reactors 23 had severe neonatal jaundice. Of the 17 males not tested 11 had manifestations which can be attributed to this enzyme defect. Of the 20 females 13 were tested and 3 were reactors—2 with clinical manifestations. Of the 10 with normal enzyme activity, 4, whose fathers were reactors, had severe neonatal jaundice. Of the 7 females not tested, 3, whose fathers were reactors, had severe neonatal jaundice.

Of the 82 infants mentioned in the introduction as exhibiting severe neonatal jaundice of unexplained ætiology, 22 were included in the present material. Of the 17 males 13 were reactors, and of the 5 females 1 was a reactor. Of the remaining 4 females who had normal enzyme activity the fathers of 3 were reactors, and in consequence the infants must have been heterozygous for this defect.

Discussion

It has been shown by previous workers that a deficiency of the erythrocyte enzyme G.-6-P.D. genetically transmitted is the common endogenous factor necessary for the development of hæmolysis upon exposure to various extrinsic substances. These substances have been listed by Larizza et al. (1960).

The present work has added another clinical manifestation which is linked to this enzyme defect. We have shown that, at least in the Greek population, in many cases of severe neonatal jaundice G.-6-P.D. deficiency was the only cause found.

Isolated reports of children with G.-6-P.D. deficiency or reduced glutathione (G.S.H.) instability and a history of neonatal jaundice have appeared in recent years.

Newton and Bass (1958) described a case of chronic non-spherocytic hæmolytic anæmia in an Italian boy who gave a history of unexplained neonatal hyperbilirubinæmia. Zinkham and Lenhard (1959) described 3 children with congenital non-spherocytic hæmolytic anæmia in 1 of whom there was also a history of neonatal jaundice. Shahidi and Diamond (1959) reported 2 brothers with chronic non-spherocytic anæmia who had severe neonatal jaundice. These workers thought that an extrinsic factor may not be necessary in the development of hæmolysis in the newborn if the G.-6-P.D. deficiency is unusually severe. Another case which is probably ætiologically similar but in which no enzyme studies were done was reported by Bruton et al. (1954). Gross et al. (1958) in their cases with G.-6-.P.D. defect include an infant with mild hæmolytic anæmia in the newborn period. One of the infants with neonatal hæmolysis attributed by Tuffy et al. (1959) to infantile pyknocytosis was an intermediate reactor.

Vella (1959), in a survey of G.-6-P.D. deficiency in the racial groups of Singapore, mentioned among the reactors 4 Chinese infants with neonatal jaundice. Smith and Vella (1960) subsequently described in Chinese infants 14 cases of kernicterus not due to incompatibility in whom G.-6-P.D. deficiency was present. In a preliminary communication (Doxiadis, Fessas, and Valaes 1960) we linked this enzyme defect to the development of otherwise unexplained severe neonatal jaundice in many Greek infants. After our communication Dr. Panizon from Sardinia drew our attention to similar observations of his (Panizon 1959). He reported 7 cases of kernicterus (5 females, 2 males) not due to isoimmunisation in whom there was either a family history of favism and/or G.S.H. instability of the erythrocytes either in the affected infant or in his parents. In a subsequent publication Panizon and Meo (1959) reported 2 male and 1 female infants suffering from the same type of neonatal jaundice who were treated with exchange transfusion.

Our results show that the G.-6-P.D. defect of the erythrocytes and the appearance of an otherwise unexplained severe neonatal jaundice are causally related. This conclusion on the one hand adds another clinical entity to those already known to be due to this enzyme defect, and on the other explains many cases of severe neonatal jaundice in the Greek population.

While so far in most instances of hæmolysis developing in persons with G.-6-P.D. deficiency the presence of an extrinsic precipitating factor was deemed essential, in more than half of our cases no such factor was found. Exposure to naphthalene was incriminated in the development of extreme hyperbilirubinæmia resulting in kernicterus in a male reactor and in a female non-reactor whose father was a reactor. The hæmolytic effect of large doses of vitamin-K analogue is well known. Some of our cases with G.-6-P.D. deficiency received a vitamin-K analogue in small doses, and although this was given after the appearance of jaundice it is our impression that it increased the rate of hæmolysis. Babies who received such treatment were among the most severely affected. This observation agrees with the results of the in-vitro tests of Zinkham and Childs (1957).

The identity of the observed enzyme abnormality with that responsible for favism or drug-induced hæmolysis is proved by the 2 infants with severe neonatal jaundice of whom 1 subsequently had an attack of favism and the other of drug-induced acute hæmolytic anæmia; moreover cases of favism were found in the families of some of our infants (see figure, families 2–5).

A deficiency of G.-6-P.D. has been observed by other workers in cases of chronic non-spherocytic hæmolytic anæmia. None of our babies or their parents have shown so far this type of anæmia, and in our material the hæmolysis in the absence of any known extrinsic factor was strictly limited to the first days of life. The question why the erythrocytes of the susceptible individuals are particularly prone to spontaneous hæmolysis at this period of life remains unanswered and is under investigation. Among the factors which could be responsible are drugs administered to the mother, hormonal transfer from mother to fœtus, and changes taking place in the neonatal

organism during the period of adjustment to extra-uterine existence.

In our highly selected material it seems that the abnormal gene had a pronounced degree of expressivity even in the heterozygous females. This should not be taken as reflecting the expressivity of the gene in the general population.

It should be noted that some newborn daughters of reactor fathers had normal G.-6-P.D. activity with the method used, but exhibited severe hæmolysis. In these infants, who were genetically heterozygous, the clinical manifestations and the results of the in-vitro test did not agree. This leads us to believe that clinical manifestations at least in the neonatal period do not depend on the degree of the enzyme defect. Such a discrepancy has also been noted by Alving et al. (1958) in adult Negro females.

Lastly, our cases of severe hæmolytic jaundice not due to isoimmunisation included a few infants clinically indistinguishable from those with the enzyme defect, where normal G.-6-P.D. activity was found in them and their families. It is therefore probable that other, as yet undetected, mechanisms may cause similar clinical and hæmatological pictures.

The large proportion of newborns with severe jaundice due to G.-6-P.D. deficiency and the possibility of effective treatment makes it imperative for the clinician practising among certain racial groups to be familiar with this condition. In these racial groups it is not enough to exclude isoimmunisation or prematurity, nor to consider as dangerous only the icterus appearing on the first day of life. Even in the absence of these well-known features kernicterus may still develop in a newborn. Such a development can be prevented only when the level of serum-bilirubin is closely watched and an exchange transfusion performed when dangerous levels are approached. This treatment not only removes bilirubin but substitutes normal red cells for those of shortened lifespan. Particular attention should be paid to families with a history of a previously affected infant or of favism or drug-induced hæmolysis; and in these a G.-6-P.D. assay should be done. In racial groups where G.-6-P.D. deficiency is prevalent, it is wise to limit as strictly as possible the use of vitamin-K analogues in both expectant mother and newborn infant.

Summary

In a third of Greek full-term infants with severe neonatal jaundice, isoimmunisation could be excluded. In most of these infants evidence of increased hæmolysis was present, and some previous siblings had been affected.

Infants with severe neonatal jaundice of unknown cause and their families were tested for glucose-6-phosphate dehydrogenase activity of their erythrocytes. In most of these infants a genetically transmitted defect of this enzyme was found; the incidence of this defect in a control group was comparatively insignificant.

This enzyme defect accounts for a significant number of cases of severe neonatal jaundice and kernicterus in Greece and probably in other countries. Such infants can be successfully treated by exchange transfusion.

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References at foot of next column

THE ROLE OF THE ERYTHROPOIETIC HORMONE IN ANÆMIA

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THE concept of a humoral mechanism controlling regeneration of red cells after hæmorrhage was first put forward by Carnot and Deflandre (1906) as a result of experimental studies on rabbits; but during the next forty years many attempts to reproduce their findings met with failure, or at best, with inconclusive results. The alternative view that anoxia of the bone-marrow provided the stimulus to increased erythropoiesis was generally accepted until Rosin and Rachmilewitz (1948) showed that in marrow culture anoxia arrested rather than stimulated erythropoiesis. This finding strongly suggested that, if anoxia was the effective stimulus, it operated through some intermediary humoral mechanism. Reissmann (1950) confirmed this by the observation that exposure of one member of a parabiotic pair of rats to a low atmospheric oxygen-tension resulted in increased erythropoiesis in both rats. Stohlman et al. (1954) later provided similar evidence from studies on a human subject with a patent ductus arteriosus. The patient had pulmonary hypertension with reversal of the shunt through the ductus, producing anoxia of the lower half of the body only. Polycythæmia had developed with normal white-cell and platelet counts, and at necropsy the marrow from the well-oxygenated region of the body showed a similar degree of erythroid hyperplasia to that from the anoxic region.

Grant and Root (1952) reviewed the evidence for the humoral regulation of red-cell production, and subsequently many attempts were made to demonstrate, in the plasma of anæmic animals, a humoral factor which would stimulate erythropoiesis in recipients.

Such direct evidence was provided by Erslev (1953), Borsook et al. (1954), and Gordon et al. (1954) who produced polycythæmia in normal rabbits or rats by repeated injections of plasma or plasma extracts from anæmic animals. Most studies have since been carried out on rats, mice, or rabbits, but Erslev et al. (1953) demonstrated reticulocytosis in normal monkeys after the injection of plasma from anæmic monkeys. Using a variety of assay procedures, the presence or absence of an erythropoietic factor in the plasma of patients with anæmia or polycythæmia has been reported by a number of workers

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(Gordon 1957, Contopoulos et al. 1957, Gurney et al. 1957, Prentice and Mirand 1957, Korst et al. 1958); but the findings were conflicting and inconstant, particularly about the circumstances in which the factor was not demonstrable.

In a recent review, White et al. (1960) have proposed that negative findings, reported on occasions in the anæmias of infection, rheumatoid arthritis, neoplasia, and chronic renal disease, may indicate that a disorder of humoral regulation is of importance in their ætiology. Before any firm conclusion of this kind can be reached, however, it would be necessary to demonstrate far more consistent results than those published hitherto; and, moreover, to assess negative findings in the light of factors known to influence the plasma-hormone titre; to evaluate the role of possible inhibitory factors interfering with assay of the hormone; and lastly, to consider evidence of the disturbance of erythropoiesis in any such anæmia in relation to the mode of action of the physiological regulator of red-cell production. Since much of the confusion in earlier reports concerns the assay methods used, it is of some importance to re-examine the likely sources of error.

Assay Preparations

Choice of Assay Preparation

The common basis of the more sensitive procedures has been the use of an animal in which erythropoiesis has been slowed before injection of the material for assay. The techniques used are: (1) slowing of body metabolism by interference with the hormonal or nutritional status of the animal; (2) toxic depression of the bone-marrow; and (3) increased supply of oxygen to the tissues by high atmospheric oxygen-tension, or by polycythæmia induced by transfusion.

Contopoulos et al. (1954) showed that the pituitary produced a factor capable of stimulating erythropoiesis in the hypophysectomised rat. It is now known that a number of hormones, including corticotrophin (A.C.T.H.), growth hormone, and thyrotrophic hormone stimulate red-cell production in such animals, and Simpson et al. (1959) have shown that their earlier results suggesting a separate pituitary erythropoietic factor were entirely attributable to A.C.T.H. Fried et al. (1956) showed that the hypophysectomised rat responded to plasma from anæmic animals with accelerated release of labelled cells from the bone-marrow, and this preparation has subsequently been widely used in the study of the erythropoietic factor in plasma (Gurney et al. 1957, Prentice and Mirand 1957, Contopoulos et al. 1957). Fried et al. (1957) showed that acute starvation slowed erythropoiesis, presumably as a consequence of the reduced metabolic requirements of the animal, and the starved rat has also been extensively used as an assay preparation (Gurney et al. 1957, Gallagher et al. 1959, Schleuter et al. 1960). A criticism of these methods is that protein-bound corticoids and thyroxine, which occur in the same plasma fraction as the erythropoiesis-stimulating hormone, might be expected to stimulate erythropoiesis; and, in the starved animal, nutrients contained in the material to be assayed would have the same effect.

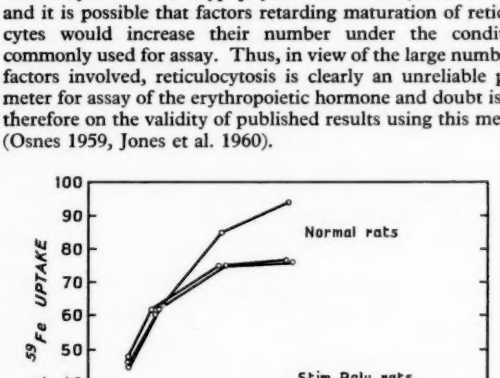
Stohlman and Brecher (1956) proposed the use for assay of rats exposed to a sublethal dose of X-rays, and Korst et al. (1958) employed animals treated with nitrogen mustard. Slowing of red-cell production occurred in each case, which was shown to be reversed to a greater extent by plasma injections from anæmic donors than by normal plasma. In both these preparations, however, a profound disturbance of nuclear metabolism and mitosis results, and the stimulation of erythropoiesis by "anæmic" plasma might be due to metabolic precursors of desoxyribose nucleic acid (D.N.A.) or general stimulants to mitosis contained in the assay material, rather than to the specific erythropoietic hormone. Korst et al. (1958) claimed to show elevated titres of this hormone in polycythæmia rubra vera using the nitrogen-mustard-treated animal, but our own observations on this disease (Penington 1960), to be reported in full elsewhere, strongly suggest that their findings are due to such nonspecific factors.

Robertson (1917) demonstrated that polycythæmia in normal animals produced by the repeated transfusion of red cells slowed erythropoiesis and Fried et al. (1957) established that this slowing could be reversed by the injection of plasma from anæmic donors. These polycythæmic animals appear to lack the physiological stimulus to erythropoiesis, and might therefore be expected to be particularly sensitive to any humoral stimulant mediating this physiological control. The polycythæmic rat was employed in the present study as the most specific of the sensitive assay preparations available.

Assessment of Rate of Erythropoiesis in the Assay Animal

The measurement of the rate of red-cell production in the assay animal has also been a source of confusion. Criteria used include red-cell count, hæmoglobin, red-cell volume, reticulocytosis, plasma-iron clearance, red-cell-iron utilisation, and marrow-D.N.A. synthesis. Red-cell counts, hæmoglobin, and hæmatocrit estimations are influenced by changes in plasma-volume, and long-lasting increase in red-cell production would be required to evoke significant changes in red-cell volume. The remainder are all liable to be influenced by hæmolysis produced by material injected for assay. Reticulocytosis and iron utilisation have been widely employed as the most convenient and sensitive techniques.

The erythropoietic hormone in whole plasma, or after partial purification, undoubtedly produces reticulocytosis in the normal rat (Rambach et al. 1957), but so also may a number of other factors. Linman and Bethell (1957) and Bethell et al. (1957) demonstrated an ether-soluble factor in the plasma of anæmic and polycythæmic patients which would induce reticulocytosis in the rat, but the red cells produced were abnormally small and had a shortened lifespan (Linman and Long 1958). This factor is distinct from the erythropoietic hormone both chemically and biologically (Penington 1960) and it seems probable from their data that it acts either by producing an additional mitosis in late normoblasts or by shortening the intermitotic interval throughout the erythroid series, a mode of action which is not consistent with its participation in regeneration in the bone-marrow under physiological conditions (Alpen and Cranmore 1959). Sodium bicarbonate alone also produces reticulocytosis in the hypophysectomised rat (Gordon 1959), and it is possible that factors retarding maturation of reticulocytes would increase their number under the conditions commonly used for assay. Thus, in view of the large number of factors involved, reticulocytosis is clearly an unreliable parameter for assay of the erythropoietic hormone and doubt is cast therefore on the validity of published results using this method (Osnes 1959, Jones et al. 1960).



Serial ^{59}Fe utilisation curves on normal and polycythæmic rats.

Polycythæmic animals received an injection of 2 ml. plasma, 24 and 48 hours before ^{59}Fe; "stimulated" animals received plasma from anæmic rats; "controls" received plasma from normal donors.

Iron utilisation, with ^{59}Fe, was used by Plzak et al. (1955) and has the advantage of providing a rapid method of assessing the rate of red-cell formation. It may be criticised since it depends on hæm synthesis which could be influenced by factors other than the erythropoietic hormone. Furthermore, if based on a single twenty-four-hour measurement, it might be argued that the result would be influenced by factors affecting release of erythrocytes from the marrow. In support of this might be quoted the curves for iron utilisation obtained by Plzak et al. (1955). Using normal rats, these workers observed that although the iron uptake in circulating red cells was greater in the first twenty hours in animals treated with "anæmic" plasma than in controls, the difference between the two groups after fifty hours was small. In a similar experiment, however, using polycythæmic rats, we have not found this to be so. The figure compares iron uptake over several days in normal and in polycythæmic rats previously injected with either normal or "anæmic" plasma. The iron uptake at twenty-four hours reflects in each group the final iron utilisation after three to five days. We have evidence from other studies (Penington and Lauchlan 1961) that ^{59}Fe uptake in the polycythæmic rat reflects fluctuations in red-cell production rather than independent variations in iron metabolism, and on these grounds we have chosen this criterion as the measure of erythropoiesis.

Methods

Technique of Assay

The following is a summary of the method, full details of which will be published elsewhere (Penington and Lauchlan 1961).

Male Glaxo-Wistar rats, weighing 110–130 g. before preparation, are rendered polycythæmic by intraperitoneal injection of packed red cells from normal donor rats of the same strain. It can be shown that the cells pass intact into the circulating blood.

Day 0.—7 ml. packed red cells.
Day 3.—3–4 ml. packed red cells.
Day 8.
Day 9. } —Intraperitoneal injection of material for assay (2 ml. daily).
Day 10.—Intravenous injection of 0·25–1 μC ^{59}Fe (ferric citrate).
Day 11.—Content of ^{59}Fe in circulating red cells determined.

In many instances a direct measurement of blood-volume of the assay rat was made on day 11, using ^{51}Cr labelled cells; in the remainder, the calculation was based on a figure for blood-volume of 7·5 ml. per 100 g. body-weight obtained in a previous series (mean of 80 determinations).

Hæmatocrit values on day 11 ranged from 55–75%; animals with values below 55% were discarded from the assay, as were those losing weight or those with evidence of intraperitoneal bleeding.

Control values were obtained in 30 rats by injection of 2 ml. normal human plasma or normal saline on days 8 and 9 and gave a mean figure for twenty-four-hour ^{59}Fe utilisation of 3·04% ± 1·06 (S.D.). No difference was found between the iron uptake in rats receiving injections of normal plasma, saline, or in those receiving no injection. The standard deviation in assay of samples was roughly proportional to the percentage iron uptake. In three separate experiments a standard dose of "anæmic" plasma was given to groups of 9 to 12 rats, and the standard deviation ranged from 13 to 16% of the mean iron uptake. Dose/response curves, determined for a number of preparations of active material from human plasma and urine, and rat plasma, all showed a positive slope. Strict quantitative assay must await the preparation of adequate quantities of purified standard material, but it is possible with the present technique to assess the relative "activity" of groups of samples.

Heparinised plasma was used and, where assay was delayed, samples were freeze-dried as soon as possible after preliminary storage at −10°C.

The results of the assay are calculated from the difference between the mean iron uptake in each assay group and the mean control value, and are expressed as a multiple of the standard deviation of the control values obtained throughout the period of study.

Chemical Methods

Active material was concentrated from plasma by a modification of the method of Borsook et al. (1954). After adjustment of pH to 5·5 by dialysis against 0·15 *M* acetate buffer, plasma was diluted with an equal volume of buffer solution, heated rapidly to the first sign of precipitation, and then kept in a boiling water-bath for seven minutes. After rapid cooling and centrifugation, the precipitate was extracted twice more with boiling buffer solution. The combined supernatant was dialysed for twenty-four hours against repeated changes of distilled water, concentrated in a rotary evaporator to approximately the original volume of the plasma sample, and then freeze-dried. The extract was dissolved in physiological saline and injected into the assay animal at a dose of 2 ml. per day.

Urine extracts were prepared by adsorption of active material on a fine benzoic acid suspension at pH 3·5, prepared by slow addition of a saturated alcoholic solution of benzoic acid to the urine sample at 4°C. After filtration and drying, the benzoic acid was dissolved in ethanol, the adsorbed protein being recovered by centrifugation. (The technique is modified from that of Davies [1958], previously applied to recover parathormone, chorionic gonadotrophin, and other mucoprotein hormones from urine.)

Results

Erythropoietic Activity of Whole Plasma in Anæmia

The erythropoietic hormone was readily demonstrated in whole plasma from patients with anæmia from various causes, with or without iron deficiency, and with hyperplastic or hypoplastic marrow.

These positive findings are summarised in table I; highly significant stimulation occurred in each case ($P < 0.01$). Of all the types of anæmia studied, only anæmia associated with renal disease gave negative results. These are summarised in table II; the assay in the case of polycystic disease is alone not clearly negative. This patient has required repeated transfusion for severe anæmia over the past fifteen months; no evidence of red-cell antibodies has been found, and the reticulocyte-count has not been elevated, but the mean red-cell survival determined by the method of Hughes Jones and Mollison (1956) using ^{51}Cr was only fifty-six days. The patient with multiple

TABLE I—ASSAY OF WHOLE PLASMA—POSITIVE RESULTS

Patient: Diagnosis	Hb (%)	Assay: Response • (× S.D. from mean control)	Animals	Significance
Iron-deficiency anæmia:				
Giant gastric ulcer M.C.H.C. 27%	33	+ 4·1	3	$P<0.001$
Hiatus hernia " 26%	42	+ 6·0	4	"
Chronic gastric ulcer " 25%	31	+ 4·5	2	"
Idiopathic " 23%	32	+15	4	"
Idiopathic " 22%	30	+16	2	"
Idiopathic " 22%	37	+10	4	"
Megaloblastic anæmia:				
Addisonian pernicious anæmia, case 1	48	+ 2·8	4	$P<0.01$
Addisonian pernicious anæmia, case 2	40	+ 7·9	4	$P<0.001$
Intestinal blind loop (B_{12} deficiency)	26†	+ 3·8	2	"
Hæmolytic anæmia:				
Autoimmune hæmolytic anæmia				
Case 1, reticulocytes 48% ..	44	+12	4	"
Case 2 " 15% ..	30	+ 4·8	3	"
Case 3 " 3% (aplastic crisis)	36	+ 8·5	7	"
Thalassæmia major	36†	+13	3	"
Aplastic anæmia:				
Pancytopenia due to triethylene-melamine for lymphadenoma	42	+ 8·0	2	"
Pancytopenia due to chloramphenicol	44	+12	3	"
Idiopathic aplastic anæmia, case 1 ..	36	+19	4	"
Idiopathic aplastic anæmia, case 2 ..	24	+34	3	"
Leukæmia:				
Acute lymphatic leukæmia	48	+ 5·8	4	"
Acute myeloid leukæmia	36	+ 5·0	3	"
Chronic lymphatic leukæmia, case 1	40	+10	4	"
Chronic lymphatic leukæmia, case 2	20	+44	3	"
di Guglielmo's disease	34	+14	4	"
Infection:				
Staphylococcal septicæmia	36	+ 5·0	3	"
Rheumatoid disease:				
Rheumatoid arthritis (erythroid hypoplasia)	40	+15	4	"
Neoplasia:				
Carcinoma of breast; carcinomatosis	44	+ 6·2	3	"

• Difference between mean % 24-hour uptake in assay and control animals expressed as multiples of standard deviation of the controls. Normal human plasma gave no activity.
† Plasma stored in the frozen state about 9 months before assay.
M.C.H.C. = mean corpuscular hæmoglobin concentration.

TABLE II—ASSAY OF WHOLE PLASMA: NEGATIVE RESULTS

Patient			Assay		
Diagnosis	Hb (%)	Blood-urea (mg. per 100 ml.)	Response* (× S.D. from mean control)	Animals	Significance
Progressive type-I nephritis	40	84	−0·8	4	Nil
Chronic type-I nephritis	40	310	+0·9	4	,,
Chronic pyelonephritis	33	339	+1·0	4	,,
Hydronephrosis; pyelonephritis	35	159	−0·6	4	,,
Malignant hypertension	29	270	−0·9	4	,,
Polycystic kidneys	34	144	+1·3	6	$0·1 > P > 0·05$
Amyloidosis	39	126	+0·9	3	Nil
Multiple myeloma	38	45	+1·0	3	,,

* Difference between mean % 24-hour uptake in assay and control animals expressed as multiples of standard deviation of the controls.

myeloma had persistent proteinuria, and at necropsy extensive deposits of myelomatous tissue were found in many parts of the body, together with atrophy of renal tubules; only slight glomerular lesions were present and there was no evidence of amyloidosis.

Assay of Concentrated Plasma Extracts

Gurney et al. (1957) demonstrated erythropoietic activity in concentrated extracts of normal human plasma, when assayed in the hypophysectomised rat. Using the plasma-extraction method employed by these workers (described by Borsook et al. 1954) I found considerable and variable loss of activity from "potent" plasma samples. Both pH and loss due to coprecipitation were important factors, but, with the modified technique described above, no significant loss of activity occurred with extraction of " potent " plasma in a series of four " recovery " experiments.

As the percentage error on assay was found to be of the order of ±15%, the recovery experiments were designed to establish whether recovery was greater than 80%. Percentage recoveries were then calculated from a dose/response curve.

Type of anæmia	*Iron utilisation (%)*		*Calculated recovery* (%)
	Extract dose 5	*Plasma dose 4*	
Hypochromic	15·8 (4)	15·5 (4)	83
Hypochromic	9·8 (3)	9·4 (4)	86
Pernicious	7·6 (4)	6·0 (4)	116
Aplastic	7·8 (4)	6·9 (4)	96

(Figures in parentheses represent animals per assay.)

Normal human plasma was concentrated by this method, and when assayed in the polycythæmic rat, no significant erythropoietic activity could be demonstrated in the extract from 50 ml. or less of plasma per assay animal. However, after venesection of a normal human subject to a hæmoglobin level of 87%, erythropoietic activity could be demonstrated (table III).

The same procedure was applied to samples from three patients with severe " renal " anæmia, and some erythropoietic activity was found, although the stimulation was slight when compared with the assay of a plasma extract from a patient with anæmia due to a bleeding duodenal ulcer (table III) or of whole plasma in the majority of cases of anæmia studied (table I). Whole plasma from the patient with polycystic disease had given the highest iron uptake of those in table II and the considerable elevation of titre of the hormone compared with the other two uræmic plasma extracts assayed (table III) is consistent with the known hæmolytic element in this case.

TABLE III—ASSAY OF CONCENTRATED PLASMA EXTRACTS

Donor			Assay			
—	Hb (%)	Blood-urea (mg. per 100 ml.)	Plasma dose per animal (ml.)	Response * (× S.D. from mean control)	Animals	Significance
Normal human plasma, 1	97		15	+ 0·3	3	Nil
,, ,, ,, 2	100		25	+ 0·6	4	,,
,, ,, ,, 3	104		25	− 0·5	4	,,
,, ,, ,, 4	100		50	+ 0·3	4	,,
Normal subject after venesection	87		20	+ 3·0	5	$P < 0·01$
Bleeding duodenal ulcer	33		1	+ 1·9	4	$0·1 > P > 0·05$
			4	+ 9·1	5	$P < 0·001$
			8	+20	3	,,
Chronic pyelonephritis	41	255	20	+ 1·5	4	$P < 0·01$
Chronic type-I nephritis	44	210	20	+ 2·7	3	$P < 0·01$
Polycystic kidneys	34	144	20	+ 5·8	3	$P < 0·001$
Malignant essential hypertension	95	68	25	− 0·8	4	Nil
Adult Fanconi syndrome	86	159	25	+ 0·9	3	,,

* Difference between mean % 24-hour uptake in assay and control animals expressed as multiples of standard deviation of the controls.

Assessment of Inhibitory Factors

The possibility of a specific antagonist in uræmic plasma interfering with assay of the erythropoietic hormone was tested in an experiment in which a potent hormone preparation was added to normal human plasma and to plasma from a uræmic patient with severe anæmia. When these were assayed under the same conditions as were used in cases of chronic renal disease with anæmia, erythropoiesis was stimulated to a comparable degree in the two.

If uræmic plasma contains a factor, or factors, which depress erythropoiesis in vivo, then it might be expected that in the occasional patient with chronic uræmia in whom anæmia does not develop there might be increased levels of erythropoietic hormone opposing this inhibition. Two such patients were studied. The first, a case of malignant essential hypertension, had been known to have renal failure for more than twelve months. The blood-urea varied between 63 and 83 mg. per 100 ml. and creatinine clearance and urea-concentration were both impaired, but the hæmoglobin never fell below 95%. The second patient was diagnosed as adult Fanconi syndrome in view of gross generalised aminoaciduria. He had been kept under observation for four and a half years, during which time, however, glomerular function was consistently impaired with the blood-urea rising steadily from 72 to 160 mg. per 100 ml. The hæmoglobin varied between 86 and 97% in this interval. In neither instance could the erythropoietic hormone be demonstrated up to a dosage of 25 ml. per rat (table III).

TABLE IV—URINARY LOSS OF ERYTHROPOIETIC HORMONE

Patient		Assay			
Diagnosis	Hb (%)	Urine dose per animal (ml.)	Fe * utilisation (%)	Animals	Significance
Hypochromic anæmia (M.C.H.C. 22%)	30	10	22	2	$P < 0·001$
		100	39	2	,,
Hypochromic anæmia (M.C.H.C. 24%)	44	1	3·6	2	$0·1 > P > 0·05$
		10	15	2	$P < 0·001$
		100	30	2	,,
Pernicious anæmia	33	10	10	2	,,
		100	26	2	,,
Progressive type-I nephritis	40	10	2·1	2	Nil
Extract (1)		100	2·8	2	,,
Extract (2)		200	2·7	2	,,
Normal urine		200	3·2	2	,,

* Assays carried out with separate group of control experiments in which %Fe uptake 2·4 ± 0·6 (24 animals).

The normal subject, bled to produce anæmia of severity comparable to that in the patient with Fanconi syndrome, showed an increase in the plasma-hormone level. From the results obtained in other types of anæmia it might be expected that the hormone would be more readily demonstrable in an anæmia due to depression of erythropoiesis than in that due to hæmorrhage.

Urinary Loss of Erythropoietic Hormone

Urine extracts obtained from patients with hypochromic and pernicious anæmia were compared for erythropoietic activity with similar extracts from a normal subject and a patient with progressive type-I nephritis. (The result of the plasma assay on this patient appears in table II.) These assays were carried out with a previous group of control experiments for which the mean iron uptake and standard deviation were 2·4% ± 0·68 (24 determinations). No activity could be demonstrated in two extracts from the patient with nephritis nor in normal urine extracts, whilst highly significant activity was found in the urine of the other anæmic patients (table IV).

Chemical Investigation of Active Material in "Anæmic" Plasma

The factor has been found to be non-dialysable, stable to limited exposure to a temperature of 100°C at pH 5·5, and to be present in the seromucoid fraction of plasma mucoproteins (prepared by the method of Winzler et al. 1948). Further concentration of activity from plasma extracts may be achieved by column chromatography on diethylaminoethyl cellulose (using a modification of the method of Rambach et al. 1958). The main component in the active fraction obtained by this procedure moves electrophoretically as an α-globulin in a "tris-borate-ethylenediamine-tetra-acetic acid" buffer system at pH 8·9 on a cellulose-acetate membrane and stains for carbohydrate with the periodic-acid/Schiff reaction. The activity is not removed from plasma by repeated extraction with large volumes of ether.

These observations are consistent with the view that the erythropoietic hormone is either a mucoprotein or exists in plasma bound to such a protein. Studies are continuing on the purification of material derived from human plasma and urine.

Discussion

The variation in titre of the erythropoietic hormone in anæmia, as found in the present study, is considerable. Many of the negative results previously reported in the anæmias of infection, rheumatoid disease, and neoplasia have been in patients with mild anæmia; and, because one important factor governing the hormone titre is undoubtedly the hæmoglobin level, such results probably reflect the limits of sensitivity of the assay procedures employed, rather than findings of significance in the ætiology of the anæmias. The present survey of the hormone in whole plasma has been confined to patients with severe anæmia, and it will be seen that the titre is elevated in every type of anæmia studied, with the single exception of that associated with chronic renal damage. The highest levels were found in cases in which erythropoiesis was considerably slowed. Thus, of the patients with hypochromic anæmia, those with the greatest iron deficiency showed the highest hormone titre; those with less severe iron deficiency and continuing gastrointestinal bleeding—hence more rapid erythropoiesis—showed lower hormone levels. These findings are consistent with the view of Stohlman (1959) that utilisation of the hormone by "active" marrow may result in low plasma levels. Factors other than utilisation, however, must also be of importance, for of the patients studied with autoimmune hæmolytic anæmia, one (case 1) had a 48% reticulocytosis with a steady hæmoglobin level, and a mean red-cell survival (^{51}Cr method) of ten days (erythropoiesis proceeding at some five times the normal rate) and yet plasma from this patient stimulated erythropoiesis in the assay animal to a greater degree than that from a patient (case 3) in a severe aplastic crisis, who had a mean red-cell survival of forty-one days. This patient had been kept under observation for three years with proven autoimmune hæmolytic anæmia, and at the time of assay had developed a profound pancytopenia with hypoplasia of all elements on marrow-biopsy. She subsequently made a full recovery.

Urinary loss of the hormone, first reported by Hodgson and Toha (1954), may be of some importance in modifying the plasma-hormone levels at higher titres, but clearly does not explain the negative results obtained in "renal" anæmia. Estimation of the hormone in urine by this technique has not proved of value in assessing the status of the hormone in the normal subject.

Whether the hormone is present in normal plasma remains uncertain. The discrepancy between the positive findings of Gurney et al. (1957), assaying plasma extracts in the hypophysectomised animal, and our own negative results with the polycythæmic-rat technique, must be due either to response of the former preparation to other hormones, or to a relative insensitivity of the latter. Fried et al. (1957) have compared these and other assay procedures, and their results indicate that the polycythæmic-rat technique is the more sensitive of the two. Furthermore, the present concentration method gives a better and more consistent recovery of the hormone from plasma, so that it is likely that the erythropoietic activity previously observed in normal plasma with assay in the hypophysectomised animal is due to circulating hormones such as corticoids, thyroxine, and possibly pituitary hormones which are not specific to erythropoiesis.

The site of production of the erythropoietic hormone remains uncertain.

Jacobson et al. (1957), from observations on the erythropoietic response of rats after total nephrectomy and bilateral ligation of the ureters, suggested that production of the hormone was intimately related to the kidney. A similar conclusion was reached by Naets (1958) and by Osnes (1958) from studies on dogs and mice respectively; but Mirand and Prentice (1957) failed to confirm the original observations of Jacobson and his co-workers, and Erslev (1958) has also presented evidence at variance with Jacobson's view. Naets (1960) has said that he could show erythropoietic activity in renal tissue extracts. Saline extracts of liver, spleen, and kidney from anæmic dogs were found to stimulate erythropoiesis in the starved rat, the renal extract being the most active of the three. All the extracts produced abscesses at the site of injection, and as the assay preparation depends on the reduced metabolic activity which accompanies starvation, the resultant inflammation is likely to vitiate the results. Moreover, Yen et al. (1960) have shown that certain purified proteolytic enzymes stimulate iron uptake in the starved rat, so that the results of assay of such crude tissue extracts are of doubtful significance. It remains uncertain, therefore, whether the kidney is itself the site of production of the hormone in the body.

The pure red-cell polycythæmia which may accompany renal carcinoma and unilateral hydronephrosis has been put forward as evidence for the participation of the kidney in the humoral regulation of erythropoiesis (Jones et al. 1960). The assay of the erythropoietic factor employed by these workers, however, was based on reticulocytosis in the normal rat, and is likely to have been influenced primarily by factors causing hæmolysis in the assay animal, and by the ether-soluble factor of Linman and Bethell (1957). This may be found in both polycythæmia vera and secondary polycythæmia, and appears to result from, rather than to cause, marrow proliferation (Penington 1960). Korst et al. (1959) have reported erythropoietic activity in the plasma of a patient with an intracranial tumour and polycythæmia, and in another with renal carcinoma, assaying these in the starved rat. More definitive studies will be required in such subjects before the significance of these clinical associations can be assessed.

Evidence derived from a study of the humoral mechanisms in human subjects with renal damage and anæmia has been meagre. It is appropriate, therefore, to review briefly the evidence relating to the cause of the anæmia in such cases:

The peripheral blood-changes in "renal" anæmia were well described by Ashe (1929) and Parsons and Ekola-Strolberg (1933) who attributed the selective depression of red-cell production to retained metabolites. Nordenson (1938), in a careful study of the condition, presented in some detail the bone-marrow changes—namely, hypoplasia of the erythroid series with an apparently normal proportion of mitoses in these cells.

Shortening of red-cell lifespan in some cases of chronic renal disease has been observed by a number of workers (Chaplin and Mollison 1953, Joske et al. 1956, Loge et al. 1958, Verel et al. 1959) but the abnormality is not constantly found, and when

present is insufficient to account for the severity of the anæmia. It is clear, therefore, that anæmia in such cases is usually due to defective erythropoiesis.

In an investigation of the erythropoietic activity of *plasma* from patients with anæmia reported by Gurney et al. (1957), using the hypophysectomised-rat and the starved-rat assay techniques, eighteen patients were studied and evidence of the hormone in plasma was obtained in eleven. No such evidence was found in the one case of chronic nephritis in this group, in one case of multiple myeloma, in two out of six with leukæmia, in two with abdominal neoplasia, or in one of seven patients with hypoplastic anæmia. In view of these variable results no definite inference could be drawn from the findings in the one uræmic patient.

Assay of *plasma concentrates* from patients with anæmia and chronic renal disease was reported by Gallagher et al. (1959), using the starved-rat technique. They were able to demonstrate plasma erythropoietic activity in only one of sixteen uræmic patients studied, whereas activity could be shown in the plasma of five other subjects, with thalassæmia major, aplastic anæmia, and " refractory " anæmia. In these five, however, the anæmia was of greater severity than in the majority of the patients with renal disease. The concentration method used was that of Borsook et al. (1954) and as loss of activity occurred in extraction, the extract from 12 ml. of plasma was injected into each assay animal. Their findings are open to criticism as there is little evidence to indicate how readily the hormone may be demonstrated by this technique in different types of anæmia of severity comparable to the uræmic cases, and furthermore no information was given as to the degree and variability of loss of activity with extraction. In the present investigation, however, assay of unfractionated plasma samples establishes that there is a considerable difference in the plasma titre of erythropoietic hormone between cases of " renal " anæmia and anæmia of many other types, and this further supports the view that the kidney, in man, is concerned in the production, or in the regulation of production, of the hormone.

If " renal " anæmia were due solely to lack of erythropoietic hormone, subnormal levels of the hormone would be present in the plasma of such patients. Normal levels cannot be detected, but the assay of concentrated plasma extracts from cases of " renal " anæmia indicates that increased levels of the hormone may occur in this condition, although much lower than in other types of anæmia. Lack of the hormone, therefore, is not the *only* factor in its causation. Evidence from in-vitro studies supporting the older view that uræmic plasma is capable of depressing erythropoiesis has been presented by Markson and Rennie (1956), but no evidence has been found in the present study to suggest either inhibition of the hormone by uræmic plasma or antagonism in patients with chronic uræmia without anæmia. Hæmolysis is certainly of importance in some cases, but whether it is the only factor additional to defective stimulation of erythropoiesis remains to be determined.

Finally, we return to Nordenson's apparently inexplicable finding in patients with " renal " anæmia of a normal incidence of mitosis in the normoblast series, associated with erythroid hypoplasia. This acquires added significance in the light of recent studies by Erslev (1959) and Alpen and Cranmore (1959) suggesting that the physiological regulator acts by stimulating differentiation of primitive stem-cells to normoblast precursors, rather than by increasing the rate of mitosis in existing normoblasts. Once differentiated, the normoblasts appear to undergo further mitosis at a fixed rate until maturation is well advanced. Great strides are being made in the purification of the erythropoietic hormone (White et al. 1960, Borsook 1959, Gordon et al. 1959) and it may therefore be possible in the near future to assess its role in erythropoiesis more fully, and also to evaluate the possible therapeutic uses of the hormone in the anæmia of chronic renal disease.

Summary

The humoral hypothesis of regulation of erythropoiesis is outlined and the difficulties of assay of the erythropoietic hormone discussed. Estimation of the hormone in plasma from patients with anæmia from various causes has been carried out using ^{59}Fe utilisation in polycythæmic rats. Consistently high levels have been demonstrated in hypochromic, megaloblastic, hæmolytic, and aplastic anæmias; and in anæmia associated with leukæmia, infection, rheumatoid arthritis, and neoplasia. No comparable increase was found in any case of severe anæmia associated with chronic renal disease.

A quantitative technique is described for concentration of the hormone from plasma. No evidence of the hormone was found in plasma from normal human subjects, but it could be demonstrated in the plasma of a normal subject after venesection. No evidence has been found of inhibition of the erythropoietic hormone by uræmic plasma, and no significant urinary loss of the hormone could be detected in a patient with " renal " anæmia, although this could readily be demonstrated in anæmia of other types. The evidence presented is consistent with the view that defective production of the erythropoietic hormone is a major factor in the production of anæmia in chronic renal disease.

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References continued at foot of next column

A HÆMORRHAGIC FEVER IN SINGAPORE

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LAST June, an outbreak of disease occurred in Singapore characterised by fever, headache, general malaise, flushing of the skin, hæmorrhagic manifestations, enlargement of the spleen, and spontaneous remission 6 or 7 days after the onset. The epidemic reached a peak in August, and by October only sporadic cases were seen. This disease resembled typical dengue fever in many respects; but, though outbreaks of dengue frequently occur in Singapore, splenomegaly and hæmorrhagic manifestations have rarely been observed. Early in the present epidemic, the disease became known locally as " Singapore splenic fever "; and the following description is based upon seventy cases, aged between 11 and 65 admitted to the department of clinical medicine at the Singapore General Hospital, and upon other cases we have seen elsewhere in the hospital. Children under 11 are not admitted to this department.

The disease affected all races, young and old alike, but most of the patients were children or young adults. The population of Singapore, however, contains an abnormally high proportion of young people (Wells and Lau 1960), and we do not feel that the age incidence of the disease suggests a significant level of acquired immunity among the older member of the population. Forty-two of our seventy cases were females, though we normally see considerably more males than females in this hospital.

Clinical Features

The presenting symptoms were as follows:

Fever .. 100%	Nausea .. 64%	Constipation .. 40%
Headache .. 80%	Vomiting .. 61%	Diarrhœa .. 14%
Body aches .. 69%	Anorexia .. 61%	Cough .. 14%

Most patients knew to within a few hours when the illness started, though in a few the onset was insidious. The temperature usually rose abruptly in the first day to a maximum between 100° and 104°F and tended to be remittent, usually remaining high for 6 or 7 days, and finally falling to normal over a period of a few hours. In a few patients the fever lasted as little as 2 and in a few others for as long as 10 days. The skin from the onset was hot and dry; and by the 3rd day there was usually a diffuse erythema over the face, trunk, upper arms, and thighs. This erythema was difficult to see in the darker skinned Indians and Malays, but could be demonstrated by blanching the skin by pressure. By the 5th day many of the patients had, in addition to the erythema, a hæmorrhagic rash varying from a few discrete petechiæ over the lower legs or abdomen to a diffuse purpura covering the whole body. The hæmorrhagic rash was usually more pronounced on the legs than on the thighs, and on the hands and forearms than on the upper arms. A peculiar feature of this rash in some patients was the appearance of small circumscribed circular areas of macroscopically and histologically normal skin, 5–10 mm. in diameter, amidst a diffuse purpuric rash like pallid islets in a purple sea. One patient presented with epistaxis, two with melæna, and a fourth had a threatened abortion.

Headache, a common initial symptom, was generally moderate, deeply situated, and dull, heavy, or throbbing; it was usually felt over the whole skull and made worse by coughing, straining at stool, noise, and bright lights. Many patients had generalised body aches and pains as well as the headache. These pains were never as severe as the bone aches characteristic of typical dengue, which have given rise to the alternative name of " break-bone fever ". Most of the patients had a mild general malaise with moderate loss of appetite, slight nausea, and mental apathy. Some of the patients were constipated, but a few had diarrhœa, and a few had a mild non-productive cough.

Few of the patients came to hospital before the 3rd day of illness and none were seen by us before the 2nd day. On first examination, in addition to the fever, hot dry skin, and rash, many of the patients had conjunctival injection, and showed lack of cooperation and drowsiness, with evidence of mild meningism—irritability, photophobia, and increased tone in the posterior neck muscles. A summary of the physical signs and results of laboratory investigations is as follows:

Erythema 59%	Inflamed tonsils .. 10%
Conjunctival injection .. 57%	Meningism 9%
Petechiæ 54%	Positive Hess test .. 93%
Palpable spleen 40%	Widal and Weil-Felix
Lymphadenopathy 20%	titres over 1/50 .. 53%

Lumbar puncture, in six patients with evidence of neurological involvement showed normal cerebrospinal fluid pressure and cytological appearances, with slightly increased cerebrospinal-fluid protein, varying from 50 to 80 mg. per 100 ml. The spleen was palpable in 40% of the patients by the 5th day of illness and was found by percussion to be enlarged in others. The pulse was usually between 70 and 100 per minute, and generally corresponded with the fever, though sometimes a relative bradycardia was observed. The liver did not appear to be enlarged by the disease, and the calf muscles were not tender.

Clinical investigation showed normal urine, and there was no anæmia. But leucopenia and thrombocytopenia developed in most patients. The lowest white-cell counts were usually found about the 6th day of illness when figures below 2500 per c.mm. were often reported, with a reduction in the neutrophil polymorphonuclears and often with atypical mononuclear Türk cells. A thrombocytopenia usually accompanied the leucopenia, and counts as low as 50,000 platelets per c.mm. were common. The bleeding-time was prolonged in some patients when the thrombocytopenia was severe, but the clotting-time and one-stage prothrombin-times were normal. A Hess-type capillary resistance test was usually strongly positive by the 7th day of illness (more than 20 petechiæ per sq. in. on the forearm after 10 minutes with the cuff inflated

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at 80 mm. Hg), whether or not there was thrombocytopenia. Bone-marrow smears in three patients with severe leucopenia and thrombocytopenia showed active marrow with no histological abnormality. The blood Widal and Weil-Felix agglutinations often showed multiple raised titres, particularly against the O antigens of *Salmonella typhi*, *S. paratyphi-B*, and *S. paratyphi-C*, and against the *Proteus mirabilis* OXK antigen. These agglutination titres, which were occasionally as high as 1/250, are uncommon in Singapore patients unless they have the specific salmonella or rickettsial infections. The titres could not be explained in these patients by previous inoculations, and all returned to normal within 2 weeks of the spontaneous remission of illness.

Blood, urine, and stool cultures for pathogenic bacteria, examination of blood for microfilariæ and malarial parasites, examination of the urine for leptospira (borrelia), and blood-leptospira agglutination and sensitised-erythrocyte lysis tests, were all consistently negative. A number of virus-isolation and antibody studies on blood and cerebrospinal fluid from these patients were carried out for us by other departments and will be the subject of separate reports.

Clinical Progress

With the cessation of fever, usually on the 6th or 7th day, the headache and other constitutional symptoms usually also disappeared. The hæmorrhagic rash gradually faded away and did not desquamate even if there had been severe confluent purpura. The leucocyte and thrombocyte counts gradually returned to normal within 2 weeks of the cessation of fever, and abnormal Widal and Weil-Felix agglutinations disappeared. The spleen, if enlarged, returned to clinically normal size in the same period. Patients commonly complained of minor degrees of lassitude and general weakness for 2 or 3 weeks after the illness, but there were no instances of undue mental depression.

Early in the outbreak, several of the patients were treated with prednisolone; and, in retrospect, knowing the self-limiting nature of the disease, prednisolone therapy may have been effective in terminating the illness and particularly in decreasing capillary fragility. In a similar illness in Bangkok, Nelson (1960) noted a dramatic response to corticosteroid therapy in moribund patients.

There were no deaths among the seventy cases studied: but, in retrospect, there was at least one patient, presenting with some features of this disease during the early weeks of the epidemic, who subsequently died.

An obese Chinese woman, aged 37; presented with fever, meningism, and drowsiness. Though the cerebrospinal fluid was normal she was thought to have a viral encephalitis. A petechial rash appeared on the 7th day of illness, and her condition suddenly deteriorated. A Waterhouse-Friderichsen syndrome was suspected and she was given 500 mg. of cortisone systemically. She died, without regaining consciousness, on the 8th day of fever, and necropsy showed no gross pathological changes except terminal aspiration pneumonia.

Epidemiology

An investigation of the first dates of onset, geographical location, and contacts of our patients produced no definite evidence about the incubation period and mode of transmission of the disease. Throughout the epidemic, cases occurred all over the island, though most of those we saw were in the densely populated urban areas. Very few of our patients knew anyone who had previously had the disease, though there were several instances where whole families simultaneously became ill. The disease affected rich and poor alike. All ages up to 65—including infants under 12 months—are known to have been affected. There appeared to be a definite indication of more cases among females than males.

Only a few of our seventy patients knew for certain that they had been bitten by mosquitoes during the weeks immediately before the onset of the disease. But, though Singapore is relatively free from mosquitoes compared to most tropical countries, we believe that most people here are in fact bitten fairly regularly by Aedes mosquitoes and that this was the most probable mode of transmission of the infection.

Discussion

At the beginning of this outbreak, some of the cases were variously diagnosed as typhoid, urban and scrub typhus, " drug rash ", idiopathic thrombocytopenic purpura, allergic Schönlein-Henoch purpura, appendicitis, and simply " pyrexia of undetermined origin ". The finding of fever with a hot dry skin, leucopenia, splenomegaly, and positive typhoid agglutinations was particularly misleading until the particular significance of the other associated findings was properly appreciated. Even later in the epidemic the occasional case remained a diagnostic problem until the full clinical picture of the disease developed.

Several fevers resembling dengue occur in South-East Asia. They differ from classical dengue mainly in the duration of the fever, and in the bone pains which are always much less severe than in dengue. Thus Van der Scheer described a " Five-day fever " in Java, and Baermann noted a " Nine-day fever " in Sumatra (de Langen and Lichtenstein 1936). Sir Leonard Rogers investigated a dengue-like fever in India which usually lasted about 6 days with a saddle-back remission (1908). He called it " Seven-day fever ", and noted that it was associated with leucopenia, a relative increase in large mononuclears in the peripheral blood, and negative Widal agglutination tests. Splenomegaly was very rare.

In our experience of Singapore fevers, this outbreak most resembles dengue. We have previously recognised two classical forms of dengue fever in Singapore which both tend to have fever lasting about 9 days. In one of these, the fever is continuous, and in the other there is a remission of fever on about the 3rd or 4th day, lasting 2 or 3 days, which is followed by a return of fever until the 9th day. In most epidemics one or other of these classical forms predominates, but both may occur as well as other shorter and less typical forms. The usual dengue fevers here have an abrupt onset with fever and severe headache. The generalised body pains are also very severe. Towards the end of the fever there may be an associated erythematous morbilliform itchy rash which is usually followed by desquamation, and all dengues here are constantly associated with leucopenia and atypical mononuclear Türk cells in the peripheral blood. The leucopenia which has long been known in dengue (Balfour 1907) and the atypical mononuclear cells described in the peripheral blood of dengue by Kisner and Lisansky (1944) are not, of course, specific findings for they occur in several other viral infections, notably measles. Hæmorrhages into the skin and mucous membranes were found in a 1928 dengue outbreak in Greece (Strong, 1942); increased capillary fragility was first described in dengue by Georgopoulos (1928), and a petechial rash appearing towards the end of the fever was noted in inoculated human volunteers (Sabin 1944 and 1952) and in a South-Pacific outbreak (Stewart 1944). McMullin (1919) described enlargement of the spleen in dengue, and Deeks described a 6-day dengue-like fever with splenomegaly in Panama (Strong 1942). Dengue in Singapore is sometimes associated with meningism and, when this is pronounced, lumbar puncture may reveal a mild lymphocytic pleocytosis with increased protein in the cerebrospinal fluid.

In the rainy season of 1954 an outbreak of serious, frequently fatal, febrile hæmorrhagic disease was reported among children

COMPARISON OF CLINICAL FEATURES OF DENGUE AND HÆMORRHAGIC FEVERS IN SINGAPORE, AND HÆMORRHAGIC FEVERS IN THE PHILIPPINES, THAILAND, AND KOREA

Clinical features	Singapore dengue fever	Singapore hæmorrhagic fever	Philippines hæmorrhagic fever	Thailand hæmorrhagic fever	Korea hæmorrhagic fever
Onset	Abrupt	Abrupt	Abrupt	Abrupt	Abrupt
Average duration of fever	9 days	6–7 days	?	?	6 days followed by toxic stage
Headache	Always severe	Usual, moderate	?	Usual	Always severe
Nausea and vomiting	Sometimes	Common	Common	Common	Usual, severe
Petechial rash	Rare	Common on 5th day	Common on 3rd day	Common on 3rd day	Common in toxic stage
Diffuse purpuric rash	Nil	Uncommon	Common	Rare	Uncommon
Abdominal pain	Rare	Rare	Common	Common	Usual
Gastrointestinal hæmorrhage	Never	Rare	Sometimes	Common	Very common
Mortality	None	Less than 1%	10%	8–23%	3–15%
Splenomegaly	Rare	40%	Rare	5–10%	Uncommon
Hepatomegaly	Nil	Nil	Nil	45%	Nil
Leucopenia	Usual	Usual	Uncommon	Uncommon	Nil (usually a pronounced leucocytosis)
Thrombocytopenia	?	Usual	Usual	Usual	Usual
Positive Hess test	Common	93% on 4th–5th day	Usual on 2nd–3rd day	Usual on 2nd–3rd day	More than 90% in toxic stage
False positive Widal and Weil-Felix titres	Nil	Common	?	Nil	Nil

in Manila (Quintos et al. 1954), and similar cases were noticed at the same time in Bangkok (Hammon et al. 1960a). Larger epidemics occurred in Manila in 1956 and Bangkok in 1958 (Nelson 1960), during both of which Hammon and his co-workers (1960a) succeeded in isolating from the blood of these cases four separate strains of dengue virus (types 1, 2, 3, and 4), Chikungunya virus, and one or more additional and as yet unnamed viruses. Though there were several similarities in the clinical features of the outbreaks in the Philippines and Thailand, there were also several noticeable differences (Hammon et al. 1960b, Hammon 1960c). These are summarised in the table, together with the main clinical features of the Singapore outbreak of hæmorrhagic fever, of typical Singapore dengue fever, and of Korean epidemic hæmorrhagic fever (Powell 1953, Barbero et al. 1953). At necropsy, the characteristic findings in the Philippines and Thailand cases were œdema and petechial hæmorrhages in almost all tissues including the heart, a small amount of blood in the intestines, coffee grounds in the stomach, and amber or blood-tinged fluid in the serous cavities. Hammon et al. (1960b) also noted that pale normal skin remained in small blotchy irregular areas amid the deep red skin blush of some of the Philippine patients, a finding similar to that in some Singapore cases.

In the present outbreak, the petechial rash, splenomegaly, and false-positive typhoid and typhus agglutinations are all at variance with our previous experience of Singapore dengue, and though the durations of fever in typical dengue overlap those in the hæmorrhagic disease, the average duration of 6 to 7 days of the latter is 2 or 3 days shorter than the typical dengue fever. The diagnosis of dengue is usually a clinical one, rarely proven by the isolation of the causal virus. Diagnosis is easy during an epidemic and in typical cases, but the mild, sporadic, and atypical cases are rarely diagnosed with certainty. Typical cases of dengue in Singapore have not always been completely investigated, but such clinically obvious features as a petechial rash and splenomegaly could not have escaped notice in previous epidemics here. Many dengue cases here have had blood Widal and Weil-Felix agglutination tests as part of the routine investigation of undiagnosed fever, and it also seems unlikely that the previous occurrence of false-positive titres in dengue here would have been missed. Platelet counts however, have not often been done in dengue here, and we cannot say whether thrombocytopenia is characteristic of Singapore dengue.

From the descriptions of Hammon et al. (1960b) and Nelson (1960), summarised in the table, the hæmorrhagic rash clearly occurred earlier in the Philippines and Thailand cases than in those in Singapore, and the hæmorrhagic manifestations appear to have been generally less severe in the Singapore cases. Certainly, the mortality in Singapore was far less than that reported in the Philippines and Thailand. These differences are unlikely to have been due to widespread partial immunity to the disease in the Singapore population, because there is no evidence of significant mortality even in young Singapore children who had the disease. The Singapore outbreak is therefore a distinct clinical entity, although its similarities to typical dengue and the hæmorrhagic fevers of the Philippines and Thailand suggest a similar viral cause, presumably infection by a specific virus of the dengue group.

The epidemic hæmorrhagic fever which occurred in 1951 among United Nations personnel in Korea (Powell 1953, Barbero et al 1953) was previously known to the Russians as " epidemic hæmorrhagic nephrosonephritis ", to the Japanese as " Manchuria or Songo fever ", and may be similar to the " Yempyeng " described in Korea by Baldocks in 1894 (Rogers 1908). It appears to be an entirely different clinical entity from the recent epidemics in the Philippines, Thailand, and Singapore.

Though the onset of the Korean illness was similar, with the abrupt onset of fever, usually lasting about 6 days, associated with headache, generalised muscular pains, conjunctival injection, and a pronounced skin flush, the Korean fever was characteristically followed by a second stage of acute toxic collapse lasting until the 10 to the 14th day. During this second toxic stage hæmorrhagic manifestations occurred with petechial hæmorrhages, epistaxes, sometimes hæmatemesis and melæna, and usually with increased capillary fragility and thrombocytopenia. Leucocytosis was common, often amounting to a leukæmoid reaction, with the appearance of many early cells of the granulocytic series, atypical lymphocytes, and up to 15% of monocytes in the peripheral blood. Renal involvement with some uræmia was constant and appeared to be one of the main causes of death. The toxic phase following the cessation of fever, and particularly the renal involvement, distinguish Korean hæmorrhagic fever from the varieties in South-East Asia.

Summary

An outbreak of hæmorrhagic fever in Singapore is described. The illness usually lasted 6 or 7 days and tended to be associated with increased capillary fragility and thrombocytopenia. There are many clinical similarities between this hæmorrhagic fever, dengue fever, and recently described hæmorrhagic fevers in the Philippines and Thailand, and it is suggested that the Singapore outbreak is probably caused by a hæmorrhagic variant of dengue virus. Unusual features of the disease were enlargement of

the spleen and the occurrence of false-positive Widal and Weil-Felix agglutinations.

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TREATMENT OF LEAD POISONING WITH INTRAMUSCULAR EDATHAMIL CALCIUM-DISODIUM

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EXCESSIVE ingestion of lead by children sickens most, kills many, and leaves half the survivors mentally retarded and disturbed. The longer the exposure, the more serious is the prognosis. Adults are more commonly affected by inhaling lead-contaminated dust; children by the ingestion of lead-containing substances as a manifestation of pica. Common targets for these perverse appetites may be cot paint, windowsills, peeling plaster, or leaden toys (Chisholm and Harrison 1956, 1957, Millichap et al. 1952).

Although most cases of lead poisoning are preceded by pica, all pica does not lead to lead poisoning (Byers 1959, Chisholm and Harrison 1956, 1957, Cohen and Ahrens 1959, Millichap et al. 1952, Travers et al. 1956). Pica, which should be asked about routinely, may provide the first clue leading to a diagnosis of lead poisoning. Parents usually omit to mention this abnormal nibbling-at-the-cot because they consider it part of the "teething stage" through which we are all expected to pass and then "grow out of". Parents should be warned to report pica immediately. The treatment of pica by appropriate means (Lanzkowsky 1958, Mellins and Jenkins 1955) and the removal of the source of lead to eliminate re-exposure will then prevent serious lead intoxication.

Most manufacturers are aware of the dangers of lead paint and avoid its use in nursery furniture. Some parents, however, do not know of this danger. After long-continued nibbling by its occupant many a cot painted in a moment of paternal enthusiasm with a lead-containing paint has produced disastrous lead poisoning.

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Incidence

Lead poisoning, prevalent in North America, is a reportable disease in Baltimore. A municipal ordinance compels the owner of a dwelling in which paint is found with a lead content in excess of 1% to remove all lead-containing paint within ten days (Bradley 1960). Furthermore, paint containing more than 1% of lead must bear a label that it is harmful if eaten. Such paint should not be applied to interior surfaces of a dwelling house or a place used for the care of children, or to windowsills, toys, cribs, or other furniture (Taylor 1960).

Only about 30 cases have been reported in Great Britain (Giles et al. 1955, Gillet 1955, Marsden and Wilson 1955, Millichap et al. 1952, O'Donohoe 1956, Travers et al. 1956, Roxburgh and Haas 1959). But obviously there are many cases that have not been reported, for in five years (1954–58) 12 children died from lead intoxication (Corkindale 1960).

The Factory Act states that all paint with a lead content of 5% or more must be labelled as "containing lead". The Ministry of Health are aware of the hazards to children from chewing lead-containing paint, as also are the furniture and toy manufacturers. There is at present no legislation in England prohibiting lead or controlling the lead content of paint used on children's furniture or toys.

The absence of a reliable analytical test for the presence of lead in small quantities which would be necessary if a legal minimum were prescribed is one of the drawbacks to attempted control by legislation (Taylor 1960).

Symptoms

The average toddler takes about three months to nibble away enough lead-containing paint to produce symptoms. During this latent symptom-free period lead is being distributed to the soft tissues, especially the brain; from these it is transferred to the bone. Reversal of the process may take place in summer, or in the presence of acidosis, with sudden increases in circulating toxic lead (Byers 1959). Thus these children without symptoms are in imminent danger and must be treated (Chisholm and Harrison 1956, 1957).

The early symptoms are protean: a toddler may present as a pale irritable constipated colicky child who refuses to play, refuses to stand, or refuses to eat—but will nibble away at windowsill, cot, or peeling plaster. If this stage is not recognised, bizarre behaviour patterns may develop. Ominous vomiting heralds the final stage of lead encephalopathy with convulsions, coma, and—if untreated—usually death. During this final phase changes appear in the cerebrospinal fluid.

Diagnosis

Lead poisoning must be diagnosed early. In all cases of pica, with or without the symptoms already mentioned, the diagnosis will be established by finding a blood-lead level above 50 μg. per 100 g. of blood (Bradley et al. 1956, Chisholm and Harrison 1956, 1957), or an increase in urinary lead excretion above 80 μg. per litre per twenty-four hours (Byers 1959).

But these tests take time and they need special lead-free apparatus for collecting samples and for testing. The screening aids listed in the table have been found useful in making a presumptive diagnosis.

DIAGNOSTIC AIDS IN LEAD POISONING

Diagnostic aid	Probability of positive result (%)	Reference
Pica	90–100	Chisholm and Harrison (1956, 1957), Cohen and Ahrens (1959), Mellins and Jenkins (1955)
X-ray abdomen for radiopaque material	30	Byers (1959)
X-ray changes in long bones	30	Byers (1959)
Glycosuria with normal blood-sugar	Very often	Roxburgh and Haas (1959)
Basophilic stippling	18	Byers (1959)
Coproporphyrinuria (ether extract)	60	Byers (1959), Benson and Chisholm (1960)
Coproporphyrinuria (ether and hydrochloric acid)	100	Benson and Chisholm (1960)
Urinary δ-amino-lævulic acid	100	Hueger-Aronsen (1960)

Treatment

Early recognition, before the onset of encephalopathy, with the prevention of further exposure to lead may be sufficient, but if the blood level of lead is over 50 μg. per 100 g., steps should be taken to assist the excretion of lead. Edathamil calcium-disodium is the calcium chelate of disodium ethylenediamine-tetra-acetic acid. When given orally or by injection the calcium is readily displaced by the lead to form a non-toxic non-ionised but soluble form of chelated lead readily excreted by the kidneys. The dosage recommended by one of the manufacturers of edathamil (Riker Laboratories 1959) is 1 g. per 30 lb. body-weight per day (70 mg. per kg.). One ampoule (1 g.) is diluted with 250–500 ml. of injection of sodium chloride B.P., and half the daily dose administered by intravenous drip over a period of one hour, twice daily for five days. This is a formidable procedure for children requiring hospital admission. The infusion of relatively large amounts of fluid may well prove dangerous to a child whose brain is already so œdematous that unless the raised intracranial pressure be reduced by intravenous hypertonic urea (Katz 1960) or by surgical decompression (Chisholm and Harrison 1956, 1957, MacLaurin and Nichols 1957), death may ensue.

Subcutaneous infusion (Bessman et al. 1954, O'Donohoe 1956) has similar disadvantages. Oral therapy has been used with success in mild cases, but the amount of lead excreted in the urine is much less than with parenteral therapy (Bradley and Powell 1954) and this treatment is unwarranted in the acute case.

The home care section of St. Mary's Hospital pædiatric department, where intravenous edathamil was first used in Great Britain by Giles et al. (1955), have now changed to the simpler intramuscular technique. This method produces as good an excretion of lead as the intravenous injection (Chisholm and Harrison 1956, 1957), but its use does not appear to have been reported in this country.

The first case was treated at home to the delight of the mother and child. Edathamil was dispensed as a 5% solution (50 mg. per ml.) with 0·5% proeaine and 0·5% chlorocresol. The dosage used in the milder first case was 35 mg. per kg. per twenty-four hours, and in the more severe second case 75 mg. per kg. per twenty-four hours—both for five days.

The intramuscular injection into the buttock caused no local reaction or pain. In both children there was an increased excretion of lead with a decrease in the blood-lead levels and rapid clinical improvement.

Byers (1959) recommends that the bowel be clear of lead salts before administration of edathamil.

Chisholm and Harrison (1956, 1957) have suggested that for all cases a 20% solution of edathamil should be given (75 mg. per kg. per twenty-four hours) for five days; and they repeat the course after fourteen days if: (1) the blood level of lead remains above 100 μg. per 100 g. of blood, (2) the urine-coproporphyrins exceed 250 μg. per twenty-four hours, or (3) serious neurological disturbance is still present.

Prognosis

Byers (1959) comments that with adequate treatment half or more of the victims of lead poisoning should be returned to competitive life. But once encephalopathy has occurred, or once the early case is re-exposed to lead, the incidence of permanent mental sequelæ rises so much that in one series Mellins and Jenkins (1955) found 14 out of 15 survivors were mentally affected. Byers (1959) reported a satisfactory outcome in only 6 out of 17 cases of encephalopathy. The mortality-rate once encephalopathy has occurred is about 25% (Byers 1959, Mellins and Jenkins 1955).

The urgency of early diagnosis and treatment cannot be overemphasised.

Case-reports

Case 1.—A boy, aged 16 months, had anorexia for five months. He had been pallid for four months; and for one month he had been irritable, with screaming attacks, and had refused to stand.

The home care unit was called to the house to see him as a case of anæmia, and the diagnosis of lead-poisoning was immediately suggested when we saw a pale, irritable, and miserable child, sitting vacantly in a cot whose paintwork appeared to have been scraped off in many places. He had been chewing at the cot for the past six months. The mother attributed this to " teething ", and thought it was probably good for his gums. The cot had been repainted about eight months previously using a pot of cheap paint.

Investigations.—X-ray abdomen, radiopaque substance present; X-ray lower end of femur, possible slight increase in density. Hæmoglobin 8·3 g. per 100 ml. A few stippled cells were seen. Urinary lead excretion, 130 μg. of lead per litre; blood-lead, 430 μg. of lead per 100 g. Scrapings from the cot contained 6·5–10% of lead.

Progress and treatment.—' Dulcolax ' was given, and a repeat X-ray two days later showed no abnormal radiopacity. Iron therapy was begun, and the mere stopping of further ingestion of lead appeared to have a beneficial effect, as the child became less irritable and ate better. As there was a possibility that the initial high blood-lead level might have been due to lead contamination from the syringe, the estimation was repeated a week later, using special lead-free syringes and containers; a blood-lead level of 100 μg. was found, the urinary excretion of lead remaining at 130 μg.

Edathamil in a 5% solution in a dose of 35 mg. per kg. was given by intramuscular injection in 2 doses daily for five days at home. A repeat estimation of urinary lead showed the excretion had increased to 430 μg. per litre. The child responded well clinically, and soon became his usual pleasant self, eating well, starting to walk about, to speak again, and to re-establish social relations with siblings and mother.

A repeat blood-lead a month later showed 70 μg. per 100 g.; the urinary excretion was 24 μg. per litre. When seen three months after treatment he appeared a pink happy normal toddler with a hæmoglobin of 9·6 g. The pica stopped soon

after the administration of iron, although after six weeks the hæmoglobin level was only 8·3 g.

Case 2.—A boy, aged 2 years, had had anorexia for a month, attacks of vomiting for three weeks, and ataxia for three days. Questioning of the parents elicited a history of pica for past six months, the child eating coal, paint, and sand, and licking leaden toy soldiers. He was pale and irritable.

Investigations.—Hæmoglobin, 8·2 g. per 100 ml.; punctate basophilia, 2%. Urine, glucose+. X-ray of limbs, normal. Blood-sugar, 85 mg. per 100 ml. Cerebrospinal fluid, 5 lymphocytes per c.mm., protein 85 mg. per 100 ml. Coproporphyrin present 1/65. Blood-lead, 360 μg. per 100 g.

Progress.—This boy was admitted for glycosuria, and when pica was found to be present, lead poisoning was suspected. The diagnosis was confirmed, the source of the lead being the leaden toy soldiers. A 5% solution of edathamil was injected intramuscularly to a total of 75 mg. per kg. per twenty-four hours, divided into 4 equal doses, for five days. He stopped vomiting, and eventually made a complete recovery. Pica stopped on admission to hospital. One month later blood-lead was 35 μg. per 100 g. When seen three months later, he appeared a perfectly normal child, with a hæmoglobin of 10·5 g.; though stippled cells are still present.

Discussion

These two cases confirm the efficacy and safety of intramuscular administration of edathamil. In the milder cases, home therapy is possible. The presence of encephalopathy warrants immediate hospital admission.

In case 1, the prevention of further ingestion of lead brought about clinical improvement; but, because the high blood level of lead was considered dangerous, edathamil was given intramuscularly with good response. The pica ceased in both children, but the effect of iron therapy remains uncertain.

Summary

Pica should suggest to the clinician the presence of lead poisoning. The protean symptoms and the value of various screening tests are discussed to emphasise the importance of early diagnosis and treatment. A simple intramuscular regimen using a 5% solution of edathamil calcium-disodium with 0·5% procaine is both effective and safe, making early lead poisoning another illness easily treated at home.

I should like to thank Dr. Reginald Lightwood and Dr. J. N. Montgomery for permission to publish case 1, and Dr. Ursula Shelley and Dr. M. P. W. Godfrey for permission to publish case 2. Special thanks are also due to the home care nursing staff who made this home treatment possible.

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DIET RICH IN UNSATURATED FAT

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INCREASING use is being made of unsaturated-fat* diets to lower serum-cholesterol levels but long-term trials will be necessary to define the place of such a diet in the prevention of the degenerative vascular diseases. For conditions characterised by high cholesterol levels, however, such as idiopathic hypercholesterolæmia, dietary treatment has now passed the trial stage. If cholesterol and β-lipoprotein lipid are to be kept at the lowest possible levels for long periods, the diet should be suitable for use at home. Various diets have recently been described: Malmros and Wigand (1957), working in Scandinavia, used special foods containing corn oil; Gordon and Brock (1958) in South Africa used naturally occurring foods, rich in unsaturated fatty acids; Olson et al. (1958), in the United States, used either fat-free or low-fat diets to which safflower, corn, cotton-seed, or soya-bean oil was added; and Pilkington et al. (1960) in Great Britain also used a low-fat diet and gave the unsaturated fat in the form of soya-bean oil.

For the past 2 years we have been engaged in a controlled trial of a diet in which the unsaturated fat is corn oil which contains about 50% of linoleic acid (Hilditch and Jasperson 1959). When given in hospital the diet was effective in lowering the serum-cholesterol and β-lipoprotein-lipid levels in diabetic children (Salt et al. 1960). Fifteen children (fourteen with diabetes mellitus and one with idiopathic hypercholesterolæmia) have now been taking a similar diet at home for periods ranging from 5 months to 2 years. Only one child stopped taking the diet, and this was because of domestic difficulties. This paper describes in detail the diet used in this trial, the outcome of which will be reported in a further communication.

Most of the fat is supplied as corn oil which is incorporated into special "milk", margarine, cheese-spread, and cooking oil.† The equivalent dairy foods and ordinary brands of margarine and cooking fat are excluded. An evaporated "milk" may be used as "cream", and a tinned rice pudding made with the special "milk" is also available. Table I gives the composition of the special foods. Vitamins A and D have been added to the milk and margarine.

We aim to supply about 40% of the daily calorie requirements by fat, 80–90% of this being taken as corn oil. The amount of saturated fat is limited to 10–20 g. daily, according to age, and most of this is contained in "protein foods" such as meat and egg. Table II shows those foods relatively low in fat content, and therefore suitable for the diet. Fish oils in general contain a higher proportion of unsaturated fats than do the fats of most land animals (Hilditch and Jasperson 1959) and need not be restricted. In the canning of fish, oils other than fish oil are often used, and therefore tinned fish should be avoided.

* For the purpose of this paper, an unsaturated fat contains fatty acids with two or more double bonds.

† These foods are made by Messrs. Alfonal, The Adelphi, London, W.C.2.

Table III gives an example of a day's meals for a child. These will supply about 2000 calories, 70 g. of protein, and 85 g. of fat, of which about 75 g. is corn oil. Puddings, cakes, biscuits, sauces, &c., which require fat are made to ordinary recipes, but the special margarine (or oil) is used in place of other cooking fats. Corn oil is used for all frying; the degree of unsaturation is not altered by high temperatures. Egg yolk, if used in cooking, must be reckoned in the daily allowance of saturated fat; egg white may be freely used. The diet can easily be adjusted to suit adult needs.

Most of the special foods, and foodstuffs made with them, are palatable. Inevitably, the flavour of corn oil differs from that of butter fat, but the margarine is indistinguishable from other brands, and the corn oil is quite satisfactory for frying. The least palatable of the foods is the " milk ", but our patients have usually tolerated it as a drink on its own, or in tea or coffee. The patient with idiopathic hypercholesterolæmia was given the " milk " from the age of 13 months and became so used to it that she refused to take cow's milk when it was reintroduced to her diet. On the rare occasions when the " milk " has not been tolerated, we have used a skimmed milk and made up the fat content of the diet with other corn-oil foods. For cooking, the " milk " is satisfactory.

TABLE I—COMPOSITION OF SPECIAL FOODS

—	Percentage composition			Vitamins (i.u. per ml. or g.)	
	Fat (as corn oil)	Protein	Carbohydrate	A	D
" Milk "	3·5	3·3	4·7	230	46
Evaporated " milk "	9·3	8·8	12·5	574	116
Margarine	54·6*	..	..	2680–3310	282–350
Cheese spread	18·4	18·5	2·5	..	..
Corn oil	100·0	..	..	..	..
Rice pudding (tinned)	3·5	2·1	12·2	..	..

* The total fat content of the margarine is 91%, but 30% of this is in the form of partly hydrogenated vegetable fat included to give the necessary hardness.

Except for the " milk ", which costs about twice as much as ordinary grades of cow's milk, the diet is not expensive. The foods keep for as long as normal dairy products. The " milk " is supplied in tins and, once opened, should be used within 24 hours unless refrigerated.

The main difficulty in the domestic use of the corn-oil diet arises from the growing popularity of ready-made and packaged foods. Cakes, biscuits, sauces, tinned puddings, and meats usually contain much saturated fat and are therefore unsuitable. This also applies to chocolate, ice-cream, and beverages such as ' Ovaltine ' and ' Horlicks '. The patient or his parents must be taught these facts,

TABLE II—FAT CONTENT OF SOME COMMON " PROTEIN FOODS " (FROM MCCANCE AND WIDDOWSON 1946)

—	*Fat content (grammes per oz.)	—	*Fat content (grammes per oz.)
Beef, steak, stewed	2·4	Liver calf, fried	4·1
Beef, topside, boiled	2·3	Mutton, chop, grilled, lean only	5·0
Beef, sirloin, roast, lean only	3·5	Mutton, leg, boiled	4·7
Chicken, boiled	2·9	Pork, loin, roast, lean only	5·7
Chicken, roast	2·1	Rabbit, stewed	2·2
Ham, boiled, lean	3·8	Turkey, roast	2·2
Bacon, gammon, fried	9·6	Veal, cutlet, fried	2·3
Bacon, streaky, fried	13·1	Egg, raw or boiled	3·5
Kidney, ox, stewed	1·6		

* This fat is almost entirely saturated.

Meat should be trimmed of all visible fat, and corn oil used for roasting and frying.

TABLE III—SPECIMEN DAILY DIET FOR CHILD

Breakfast:
- Cereal with special " milk "
- Egg fried in corn oil
- Bread or toast with special margarine
- Jam or marmalade
- Special " milk " to drink

Midmorning:
- Special " milk "
- Home-made biscuit or cake

Lunch:
- Lean beef
- Gravy made with corn oil or special margarine
- Mashed or boiled potato
- Green vegetable
- Rice pudding with jam or fruit (tinned, or made with special " milk ")
- Fruit-juice or water to drink

Tea:
- Bread with special margarine
- Jam, honey, or special cheese spread
- Home-made cake
- Tea with special " milk "

Supper:
- Fish fried in corn oil
- Bread with special margarine
- Fruit with special evaporated " milk " or custard made with special " milk "
- Water to drink

and the fat content of any tinned or packaged food should be found out before it is used in the diet. The only way of overcoming this difficulty will be to increase the range of the corn-oil foods. A start has been made with rice pudding; and a palatable ice-cream has been manufactured, though it is not yet commercially available.

For the occasional meal away from home, we have allowed a break from the diet; but, if meals are regularly taken out, the diet can usually be maintained. For holidays, we have advised that corn-oil foods should be eaten; but for short periods we have not insisted on the diet being rigidly kept.

Summary

An unsaturated-fat diet, suitable for use at home, is described. Most of the daily fat is taken as corn oil, which is incorporated in special foods. By using these foods palatable meals can be prepared and eaten regularly for long periods.

It is a pleasure to thank Dr. O. H. Wolff and Mr. H. B. Salt for their help in the preparation of this paper. We are grateful to Messrs. Alfonal for their gift of corn-oil foods for use in the hospital.

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NEONATAL DEATH FROM PIGMENTED COLIFORM INFECTION

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DESPITE the decline in morbidity and mortality from infection in the neonatal period, septicæmia and meningitis can still occur suddenly and unexpectedly and can still defy modern treatment. The cause is commonly a gram-negative bacillus—sometimes *Escherichia coli*, sometimes an unusual member of a group not generally regarded as pathogenic.

Two cases are described of infants dying within two days of each other at Osterhills Hospital (St. Albans City Hospital). There seems no doubt that both died of generalised infection, including meningitis, caused by an unusual pigmented strain of the cloaca group.

Bacteriology

Cloaca or *Aerobacter cloacæ* is a gram-negative motile non-encapsulated rod of the coli-aerogenes group, normally found in water and food, and sometimes in fæces. Jordan (1890) first isolated it from sewage, distinguishing it from the other coliforms by its power to liquefy gelatin. Cloacæ have been subdivided by Hormæche and Munilla (1957) into *Aerobacter cloacæ* (cloaca A) and *Aerobacter aerogenes* (cloaca B), Jordan's original strain (Hormæche and Edwards 1958).

The coli-aerogenes group do not usually produce pigment, although Bergey (1957) has mentioned a yellow-pigmented cloaca.

Topley and Wilson (1955) place all pigment-forming aerobic rods in the genus chromobacterium, and some resemble members of the coliform group. Pigmented coliforms are regarded as mainly saprophytic, but there are reports of cases where they have caused disease in man. Probably the earliest known pathogenic pigmented coliform (golden brown) was isolated in 1925 from a diseased eye, and was investigated later by Malligo et al. (1955) in a series of similar strains. These closely resembled *Esch. coli*, but the pigmentation justified their recognition as a separate species—*Esch. aurescens*.

Septicæmia due to a yellow-pigmented coliform has been described by Pangalos (1929) and Shutz and Laun (1933). *Serratia marcescens* (*Chromobacterium prodigiosum*) —red pigmented—has been reported as the cause of septicæmia (Patterson et al. 1952), meningitis (Aronson and Alderman 1943), and respiratory tract infections (Gale and Lord 1957, Papapanagioutou and Aligizakis 1959).

Clinical Reports

Case 1.—A boy born on May 29, 1958, weighed 6 lb. 11 oz. The mother had had mild toxæmia of pregnancy at 38 weeks, and labour induced 3 days before term. The baby was discharged at 10 days, weighing 6 lb. 4 oz. Next day he was readmitted, because, 12 hours after discharge, he was seen to be jaundiced and had had several left-sided fits. He appeared extremely ill; pulse-rate 180. The liver was enlarged, and the anterior fontanelle was bulging. A diagnosis of meningitis was made and lumbar puncture performed. Intramuscular phenobarbitone, followed by paraldehyde, failed to control the fits; and intramuscular oxytetracycline failed to control the infection. The baby died 48 hours after the onset.

Bacteriological findings.—Gram film showed moderate numbers of gram-negative rods. Culture yielded a profuse growth of gram-negative pigmented rods later identified by Dr. M. T. Parker of Manchester Public Health Laboratory as pigmented organisms belonging to the cloaca, group A. The organism was sensitive to chloramphenicol and streptomycin.

Case 2.—A girl born on June 5, 1958, weighed 4 lb. 7 oz. The mother was admitted as an emergency having had an antepartum hæmorrhage at 32 weeks owing to placenta prævia. Twins were delivered by lower segment cæsarean section. The first, a boy, weighing 2 lb. 10 oz., made good progress. The second breathed within 2 minutes and remained well for 5 days, when she suddenly collapsed with cerebral signs, jaundice, and an urticarial rash. She died several hours later. No laboratory tests were performed.

Postmortem Findings

Necropsies were performed by Dr. J. I. Pugh within 12 hours of death. In both infants the findings were similar.

The main pathological abnormalities were seen in the brain. The leptomeninges were free from visible exudate. The hemispheres were greatly swollen and the convolutions flattened. On the cut surface, a few petechial hæmorrhages were found in the cortex, and the white matter was transformed into a soft hæmorrhagic mass. The cerebellum, brainstem, and spinal cord appeared pale, but firm. The middle ears were dry and free from purulent exudate.

The only difference between the two babies was seen in the respiratory tract. In case 1 there was no macroscopic evidence of inflammation, but the nares and main bronchi of case 2 contained scanty yellow fluid, and the congested lungs showed consolidation. The umbilicus appeared healthy in both.

Histological appearances.—The brain showed cerebral necrotic hæmorrhagic inflammation, caused by massive invasion by gram-negative bacilli.

Bacteriological investigations.—Swabs were taken in case 1 from brain, cerebrospinal fluid, bronchus, urine, and blood; and in case 2 from brain, bronchus, liver, marrow, and spleen. Pigmented cloaca were isolated in case 1 from all but the urine and blood which were sterile, and in case 2 from all but the spleen which was sterile. *Staphylococcus pyogenes* was cultured from the bronchus of case 2. All the strains isolated from both infants were identical.

The organisms isolated were motile, noncapsulated, gram-negative rods measuring $0{\cdot}5 \times 5\ \mu$.

They grew well, with smooth round colonies, on nutrient agar at room temperature (30°C) and with larger colonies at 37°C, aerobic and facultatively anaerobic. On MacConkey medium, colonies were small; on blood-agar, they were non-hæmolytic. The cultures produced a non-diffusible yellow-gold pigment on nutrient agar at room temperature, but only a slightly yellow pigment at 37°C. The pigment was insoluble in water, alcohol, chloroform, and ether.

Discussion

After making normal good progress, both infants rapidly showed signs of severe infection. Loss of appetite, jaundice, and clinical signs of meningitis appeared within a few hours, and deterioration was rapid. The method of infection remains unknown, but the respiratory tract may have been the portal of entry in case 2.

Although the babies died within 2 days of each other, they were at no time in contact nor were they together in the same ward or nursery. No similar case is known to have occurred before or since. If there was a common source of infection, it has not been identified. That only one of the twins should have been affected by this fatal infection is remarkable since both had the same treatment and shared nurses. The twins were placed in separate incubators. This is the one difference. Case 1 was in an incubator—possibly the one used for case 2—for a few hours after birth, and this incubator, although a week had elapsed, could conceivably have transferred the infection.

The baby remained well for 10 days after leaving the incubator. Nevertheless, because it provides the only possible contact between the two babies—apart from human beings—some bacteriological studies of the incubators were made by one of us (A. M. C. U.). Swabs taken several days later from the incubator, as well as from various places in the obstetric ward, grew similar flora but no cloaca or pathogenic bacteria.

Infection by inhalation of serratia aerosol was investigated by Paine (1946) at a room temperature of 86°F and 81% relative humidity. After $2^1/_2$ hours' exposure, healthy adults experienced temporary malaise, cough, and fever. At the time of these infections, the incubator was usually kept at 80°F and 80% humidity.

In view of the striking similarity of conditions, there is the possibility of infection by aerosol in an incubator, especially in a sick or premature infant.

To investigate this, swabs, and water from the tank, were taken from time to time from various incubators. The water was mostly sterile, but when it was contaminated by non-pathogens, these were also isolated from the inside of the incubator. Recently, the later type of incubator, which has cuffs to enable the staff to feed and to handle the infant without lifting the cover, has been tested. The humidity in these is

usually kept between 60 and 70%. Settling-plates were put in the incubators and in the ward; and, at the same time, water was taken from the tank of the incubator for culture. Whatever bacteria grew, there was the same flora of non-pathogens in ward, incubator, and water; the incubator produced the fewest colonies.

These tests, done under normal working conditions, suggest that, though the latest type of incubator is safer than the old type, the possibility of aerosol infection cannot be completely excluded, and it seems advisable to keep the humidity as low as possible.

We wish to thank Dr. M. T. Parker of the Public Health Laboratory, Manchester, who kindly typed the organism and gave his helpful advice; Dr. Herta Schwabacher for testing the virulence; Dr. I. V. Pugh for his help with the necropsies; and Mr. R. Hill for technical assistance.

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PERIANAL HERPES SIMPLEX

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THE virus of herpes simplex is widespread, a large proportion of the adult population showing immunological evidence of past infection (Andrewes and Carmichael 1930). The lesions tend to appear in the embryological ectodermal tissues. In over 80% of those infected (Scott 1958) the primary invasion is subclinical, and the virus remains latent. In the remainder, the disease is characterised by a local eruption, a variable but fairly constant systemic disturbance, and a rise in the titre of specific circulating antibodies during the recovery phase. Most of these primary infections, clinical and subclinical, occur during the first 5 years of life with a peak incidence at 3. In children under 5, according to the observations of Miller et al. (1960), the clinical illness is as frequent as mumps and rubella.

Herpetic lesions arise when the latent infection is reactivated. The most familiar example is the herpetic eruption around the mouth, during acute febrile episodes. Recurrent, or secondary, herpes is characterised by a local eruption without a continuing systemic upset and without a rise in the titre of circulatory antibodies.

The two cases I report illustrate some of the clinical and epidemiological characteristics of the disease. They are of additional interest because of the rarity of primary perianal eruptions.

Case-reports

An identical twin, aged 2, was admitted on Jan. 27, 1960. A week before, when he began to cut a tooth, he had had a mild painless napkin rash. At this time his father was suffering from an influenza-like illness, during which he had two "cold sores". These lesions were slightly irritating, and the father applied zinc and castor oil ointment to them. This ointment was kept for treating the napkin rashes in the twins, and the mother used it a few days later on both twins.

Three days before admission the child woke up in the night, crying, restless, and feverish. Two days later, vesicles were noted, superimposed on the napkin rash. The fever and malaise persisted. The rash did not respond to treatment.

His twin brother, who also had had a mild napkin rash while teething, had a painful vesicular eruption on the buttocks, with fever and malaise, although he was less ill than his brother. Zinc and castor oil ointment had been applied before the rash became painful.

Perianal herpes simplex in a boy of 2.

Neither twin had previously had such a painful rash. Neither had symptoms suggestive of ulcerative stomatitis. There was no history of rectal bleeding or fissure in either boy. There was no other family history of herpetic infection, apart from the secondary herpes in the father.

On admission, the first boy was fretful and feverish (temperature 101°F), but not acutely ill. There was a raw painful red weeping area of skin extending 5–7 cm. around the anal margin, and on to the perineum (see figure). On the periphery of this erythema were numerous small ulcers, and white vesicles, 2–4 mm. in diameter. They contained clear fluid and were covered with a pearl-grey membrane. The inguinal lymph-nodes were enlarged and tender. There were no lesions in the mouth or throat.

He remained febrile and irritable for the next two days. The vesicular rash persisted for another seven days. After seventeen days, the rash had almost disappeared. For several weeks he was troubled with constipation, and once during his stay in hospital he had had rectal bleeding. No specific treatment is satisfactory for herpes; and so, apart from cleansing and toilet of the inflamed area, none was given.

Investigations

Hæmoglobin 81% (11·8 g. per 100 ml.). White blood-cells 7800 per c.mm. (neutrophils 64%, lymphocytes 34%, monocytes 2%). Urine: reaction alkaline; protein 300 mg. per 100 ml.; no cells in deposit; culture sterile. Stool culture, negative. Throat culture, no pathogens isolated.

Virus studies: fluid from perianal vesicles grew the virus of herpes simplex on egg-culture.

Complement-fixation test for herpes virus: Jan. 28, titre < 1/8; Feb. 9, titre 1/64.

The second twin was not admitted, and his vesicles disappeared before virus studies could be made. There was, however, little doubt about the herpes diagnosis of herpes simplex.

Discussion

The commonest clinical manifestation of primary herpes simplex is an acute ulcerative gingivostomatitis occurring in early childhood (Dodd et al. 1938, Scott et al. 1941). Much less often, the primary lesions occur on the skin and mucous membranes elsewhere. Herpes progenitalis in the female (Slavin and Gavette 1946), meatal herpes in the male (Slavin 1951), and keratoconjunctivitis (Gallardo 1943) have been described, and have been shown to be due to herpes simplex infection. Generalised skin

involvement—" Kaposi's varicelliform eruption "—arises when a pre-existing skin disease (usually infantile eczema) is infected with the virus (Brain 1956). Local lesions may appear on traumatised skin; and segmental skin lesions, simulating herpes zoster, have been reported by Slavin and Ferguson (1950). Very rarely fatal generalised herpes simplex infections, with widespread visceral lesions in the brain, liver, and adrenals, have been recorded in the newborn (Brain 1956, Bird and Gardner 1959).

In the two cases, primary herpes simplex infection caused perianal vesiculation with a generalised systemic upset, but without lesions elsewhere. Both followed a presumed labial herpes in the father. The lesions were confined to the site of a preexisting napkin rash. Such lesions are rare, although it is not unlikely that they may be mistaken for a common napkin rash. Brain (1956), describing the vagaries of herpetic infection, cited a case of herpes occurring on a napkin rash, but Scott (1960) has never found herpes in this situation. Miller et al. (1960), in a comprehensive study of all illness occurring in 847 Newcastle children under the age of 5, found that primary cutaneous herpes was not uncommon:

These workers recorded 118 cases of herpetic stomatitis. In 17 instances there were concomitant skin lesions and signs of more distant spread of the disease—including conjunctivitis, nasal discharge, and Kaposi's varicelliform eruption in an eczematous child. 1 child had abdominal colic, painful defæcation, and perianal lesions. 2 others had painless rectal hæmorrhage. In all these children, stomatitis was the predominant feature. There were 28 cases in the Newcastle survey in which the cutaneous eruption was the sole feature. Most lesions appeared on the lips; but a few were in unusual sites—the cheek (4), chin (3), nose tip (1), and ankle (1). None were noted on the buttocks.

Miller et al. (1960) found a high incidence of contact with similar cases in the household, especially when cutaneous lesions were the only manifestation. There was household contact in 12 out of the 28 cases.

The exact mode of infection in the twins must remain conjectural. Direct contact spread was unlikely. Spread via the zinc ointment was a strong possibility, as it is known that herpes virus can be absorbed on lipid substances, and thus could have survived in the ointment. The infection may have been transmitted via the mouth and gastro-intestinal tract, the virus finally infecting the excoriated tissues around the anus. Both children are now liable to recurrences of the infection at the original site, in response to any influence which may disturb the latency of the virus.

Summary

Primary perianal herpes simplex, occurring in identical twins, is described. The mode of infection and the general characteristics of herpes simplex infections are discussed.

I am indebted to Dr. I. M. Anderson, under whose care these patients were admitted, for his interest and for permission to report them; to Dr. W. M. Edgar and Dr. F. O. MacCallum, Virus Reference Laboratory, Colindale, for the virus studies; and to Dr. Peter Hansell for the photograph.

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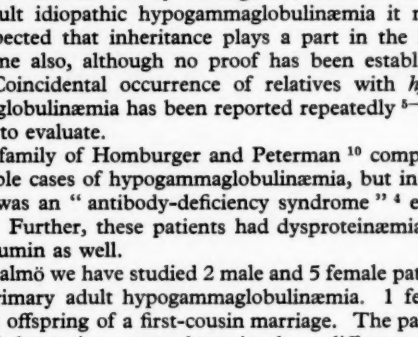
Preliminary Communication

INHERITED "ACQUIRED" HYPOGAMMAGLOBULINÆMIA

THE recessive sex-linked inheritance of congenital agammaglobulinæmia, postulated by Janeway et al.,[1] is well established through the observations of Kulneff et al.[2] and Porter.[3] Because of similarities in clinical behaviour and laboratory findings between this disease and adult idiopathic hypogammaglobulinæmia it might be suspected that inheritance plays a part in the latter syndrome also, although no proof has been established yet.[4] Coincidental occurrence of relatives with *hyper*-gammaglobulinæmia has been reported repeatedly [5–9] but is hard to evaluate.

The family of Homburger and Peterman [10] comprised 3 possible cases of hypogammaglobulinæmia, but in only 1 case was an " antibody-deficiency syndrome " [4] established. Further, these patients had dysproteinæmia and low albumin as well.

In Malmö we have studied 2 male and 5 female patients with primary adult hypogammaglobulinæmia. 1 female was the offspring of a first-cousin marriage. The parents of 6 of the patients were born in three different small geographical areas, 2 persons coming from each area. This led to further investigation of the pedigrees in the church



Pedigree showing relationship between 2 cases of adult hypogammaglobulinæmia. The linking parents have a normal serum-protein pattern.

archives. 2 female patients did in fact originate from common ancestors, born in 1780 and 1790 (see accompanying figure). These patients are 27 and 41 years old. Both have had repeated infections, mainly of the respiratory tract, since the ages of 13 and 27 respectively. Both had the electrophoretic pattern of almost complete agammaglobulinæmia. They both belong to blood-group O, rh+. The younger patient had isohæmagglutinins in the serum, but the older had none. Splenomegaly and leucopenia were absent in both cases. The disease had run a malignant course in both cases, necessitating

1. Janeway, Ch. A., Apt, L., Gitlin, D. *Trans. Ass. Amer. Phycns*, 1953, **66**, 200.
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10. Homburger, F., Peterman, M. L. *Blood*, 1949, **4**, 1085.

lobectomy for bronchiectasis in the younger patient after 10 years' illness, and producing advanced pulmonary fibrosis in the other. When the diagnosis was made and γ-globulin treatment was begun, the patients partly regained health: 1 had two normal pregnancies, and the other had normal menstruation for the first time. Agammaglobulinæmia, however, persisted throughout the observation period of about five years.

Kushner et al.[11] have described a family in which the proband and 3 of his 7 children had moderate hypogammaglobulinæmia. The affected members had splenomegaly and a tendency towards leucopenia. The proband's parents and 2 siblings were healthy. Kushner et al. concluded that this was a new variety of hypogammaglobulinæmia syndrome, possibly inherited as a dominant autosomal trait.

11. Kushner, D. S., Dubin, A., Doulon, W. P., Bronsky, D. *Amer. J. Med.* 1960, **29**, 33.

We are studying relatives of our patients and have examined blood samples from 1 sibling of the younger and 3 of the older patient as well as from parents, aunts, uncles, and several cousins. We have found nothing abnormal about them yet. Since idiopathic hypogammaglobulinæmia is very rare, our findings strongly point to an autosomal recessive inheritance. Lack of earlier observations of this kind may be due to a low gene frequency.

SUMMARY

In 2 cases of adult idiopathic hypogammaglobulinæmia the patients have been shown to be distantly related to each other. No abnormalities have so far been detected among parents or other relatives. The findings support the hypothesis of an autosomal recessive inheritance of adult hypogammaglobulinæmia.

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New Inventions

A JERKIN PLETHYSMOGRAPH

THE full-body plethysmograph has been used for several years to measure changes in body volume. These changes can be correlated with other measurements to study certain aspects of the respiratory and circulatory systems.[1] But the technique requires a rigid, airtight box with a volume of 600–1000 litres, and it demands cooperation of the subject who has to remain inside the apparatus. Thus, unless strict precautions are taken, repeatable results are difficult to obtain. Hence the method is not easily adapted to clinical or routine use.

The jerkin plethysmograph was developed to overcome some of these difficulties. It may not possess the accuracy obtainable by experienced use of the full-body plethysmograph, but the equipment is simpler, and easy to use.

The jerkin, a double-layer garment filled with air at slightly positive pressure, is put on the patient from the front, fastened at the back by a full-length zip fastener, and laced under the crutch so that it keeps its position on the body. Cross-lacing down the front allows adjustments for differences in size of the trunk (fig. 1). During respiratory movement the inner layer of the jerkin moves freely as the volume of the trunk alters, while the outer layer moves far less. These differential movements produce a change in jerkin pressure which is related to the change in trunk volume during respiration.

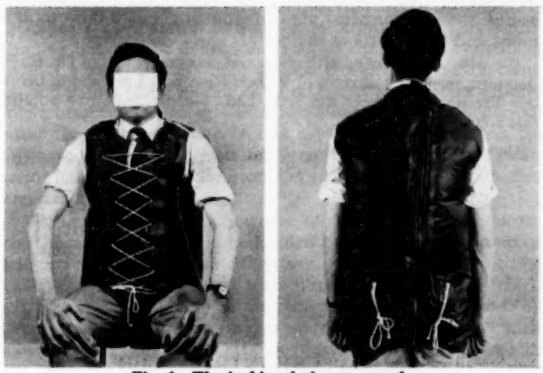

Fig. 1—The jerkin plethysmograph.

METHOD

The jerkin, filled with about 25 litres of air, is fitted to the patient, and the lacing is adjusted so that, at the end of full expiration, the pressure inside is slightly positive (about 1 cm. H_2O). At normal relaxation volume the jerkin pressure will rise to about 2 cm. H_2O, and during quiet respiration the pressure rises above this level to about 2·5–3 cm. H_2O. These pressure changes are measured with an electromanometer.[2]

For some purposes there is no need to know the precise relation of jerkin pressure to trunk volume. In others, the trunk volume and jerkin pressure can be correlated by having the patient inspire known volumes of gas, starting from various levels of chest expansion. An alternative method is to insert a thin-walled bag between the chest and the inner layer of the jerkin; the bag is partially inflated with known quantities of air and the changes in jerkin pressure are recorded. The characteristic of the jerkin is linear over a range of several litres, with a slope of about 1·5 cm. H_2O per litre of air inspired. The patient does not notice this pressure, and it is unlikely to cause significant change in respiratory function.

APPLICATIONS

Continuous monitoring of respiratory movement is the simplest application of the jerkin plethysmograph. The patient can wear the garment for several hours without discomfort. Changes in posture may cause artefacts, but these are easily recognised. The frequency and severity of coughing are also recorded (fig. 2). This means of following respiratory move-

Fig. 2—Record of jerkin pressure, showing the pressure swings during quiet respiration, with coughing at the marked points. (Inspiration upwards, time marker at 1 sec. intervals.)

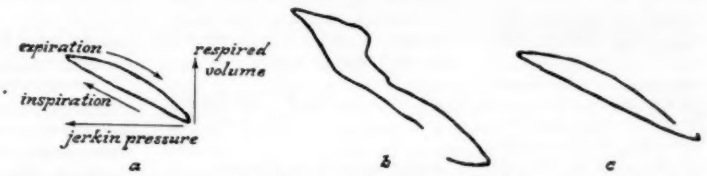

Fig. 3—Volume-volume loops (*a*) in a normal subject, (*b*) in a patient with bronchospasm, and (*c*) in the same patient after inhaling isoprenaline.

1. Comroe, J. H., Botelho, S. Y., Du Bois, A. B. *J. appl. Physiol.* 1959, **14**, 439.
2. Scott, P., Williams, K. G. *J. Physiol.* 1960, **151**, 4P.

ment can be applied for children and babies. In contrast, the jerkin can be used to detect changes in trunk volume, which may be related to gas exchange and blood-flow to and from the trunk, during breath-holding and controlled apnœa.

When the jerkin is used in conjunction with a recording pneumotachograph, the change in volume detected by the jerkin can be compared with the flow of gas in and out of the lungs. Further, if the output of the pneumotachograph is integrated, the actual volume of gas breathed can be compared with the changes in trunk volume. The instantaneous values of these volume changes can be continuously compared by displaying the two measures along perpendicular axes on a cathode-ray oscilloscope. This gives a "volume-volume" loop corresponding to each respiratory cycle [3]; a normal loop is shown in fig. 3*a*. Qualitative changes in the shape of this loop may be obtained from patients with respiratory disease (fig. 3*b*). The usefulness of the technique is further shown by the loop in fig. 3*c*, obtained after the same patient had inhaled isoprenaline.

The value of the jerkin plethysmograph in clinical investigation cannot be assessed until large-scale studies of patients have been made. Work is also in progress on the use of double-walled flexible garments for investigating blood-flow in the limbs and other parts of the body.

We wish to acknowledge the help and encouragement of Dr. C. F. Bareford, managing director of Vickers Research, Ltd., and to thank the directors of Vickers Research, Ltd., for permission to publish this account.

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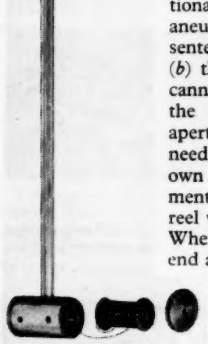
A LIGATURE INTRODUCER

THIS instrument, made of brass, consists of a drum closed with a screw cap and containing a spool running on a spindle, the whole screw-mounted at right angles on a thin tube with its end turned to fit standard Luer needles. Thread carried on the spool is led down the tube and out through the hollow needle, the end of which is bent into a J with the bevel cut off (see figure).



The ligature introducer. Drum: diameter 1·5 cm., length 3 cm. Handle: diameter 0·6 cm., length 15 cm. Needle: no. 14 (gauge 23).

Designed for work on small animals, the instrument may be used to pass a ligature round any structure in a confined operational field. Its advantages over an aneurysm needle are: (*a*) the thread is presented at the extreme tip of the introducer; (*b*) the thread, being completely enclosed, cannot foul any projection in the field; (*c*) the hollow needle passes through an aperture smaller than will take an aneurysm needle; and (*d*) it may be used to create its own tunnel. A disadvantage of the instrument is that it is tiresome to reload; but the reel will carry 30 m. of no. 0 braided silk. When loading, the thread is waxed at the end and passed through the unbent needle from the tip. If the thread breaks, the broken end may be passed through the needle on a piece of fuse wire bent on itself.

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3. Williams, K. G. Proceedings of the Third International Conference on Medical Electronics. London, 1960. In the press.

Reviews of Books

Clinical Pharmacology

D. R. LAURENCE, M.D., M.R.C.P., senior lecturer in applied pharmacology, department of pharmacology, University College, and medical unit, University College Medical School, London; R. MOULTON, M.D., lately research assistant, medical unit, University College Hospital Medical School, London. London: J. & A. Churchill. 1960. Pp. 460. 32*s*.

AUTHORS of books on applied pharmacology are in danger of being considered too academic by clinicians or too empirical or superficial by pharmacologists; and in fact it is impossible to write a textbook for medical students on this subject without some compromise. Dr. Laurence and Dr. Moulton have succeeded admirably in maintaining a balance between the pharmacology of drugs and their use in treatment; and they have also written a book which is a pleasure to read. The layout of the book is orthodox, drugs being generally grouped on the basis of their actions. The space given to various drugs is proportional to their importance to the doctor and there is a useful chapter on general pharmacology and on the unwanted effects of drugs. Scattered through the text are some useful tables, and the authors have made a point of including direct quotations from original sources, which add variety to the style. Each chapter has some key references from the literature on the drugs discussed.

The chapters on hypotensive and vasodilator drugs and on digitalis are particularly good. The section on hypnotics is rather short considering the importance of this group of drugs and might reasonably be expanded in future editions.

This is an excellent book, quite one of the better texts on applied pharmacology. It should be read by every medical student and would be useful and entertaining reading for the practising physician.

Anaerobic Bacteriology in Clinical Medicine

A. TREVOR WILLIS, PH.D., M.B., lecturer in bacteriology, University of Leeds. London: Butterworth. 1960. Pp. 176. 30*s*.

MEDICAL bacteriologists, especially those who do the routine diagnostic work for hospitals, generally have too much work to do in too little space with too little technical help. Probably for these reasons, the pathogenic anaerobes have not had the attention they deserve in routine hospital practice. These microorganisms, until the past ten years or so, were almost a special province for enthusiasts and experts only because of certain difficulties in their cultivation, isolation in pure culture, and identification. Working with Professor Oakley, Dr. Willis not surprisingly became both an enthusiast and an expert in this field of work. He concluded that the difficulties had been overrated, and set himself the worthwhile task of writing a book on methods, which would help others to undertake work that was worth doing and was increasingly being recognised as important. Gradually, non-technical issues kept pushing their way in to Dr. Willis's book and the completed work deals excellently not only with technique but also with the essential minima necessary to form a fair picture of the properties and significance of the clinically important anaerobic bacteria. The result is a book of great value and accuracy and of commendable clarity and brevity. It does not claim to include everything, but it certainly contains enough to transform the approach which most medical bacteriologists now make to the pathogenic anaerobes. The book may be unreservedly commended.

Lectures on the Scientific Basis of Medicine

Vol. VIII, 1958–59. Postgraduate Medical Federation, University of London. The Athlone Press. 1960. Pp. 467. 45*s*.

BOTANISTS, biologists, virologists, are allied with pathologists and physicians in contributing this new volume in the well-known series. Here the keen doctor can read the revelations of the latest refinements of modern electron microscopy and can contemplate the deeper problems of gamma-globulins, in chapters which require concentration but which repay the effort.

Fortunately many of our clinical investigators are themselves contributing to basic scientific developments, and Stuart-Harris's chapter on the adenoviruses with those of Cope (adrenals), Wrong (sodium), and Walshe (hepatic coma) will be of special interest to the practising doctor, as will those of Harrison (pulmonary hypertension), and Lynne Reid (bronchitis). Byrom presents views on hypertensive encephalopathy in the rat, but it is doubtful whether his ideas on vascular spasm are completely transferable to hypertensive disease in man. A lesson from a rare disease is included in hyperoxaluria. The critical review by Miles on the vascular phenomena of inflammation is distilled from an enormous investigative experience. While complete reading of every chapter would reward the industrious reader, it is more likely that individual effort will be confined to specific chapters with no more than a skimming of others. It is a little sad to realise that our basic biological sciences are developing beyond the capacity of any single mind.

The Composition of Foods

Medical Research Council Special Report Series, no. 297 (3rd revised edition of Special Report no. 235). R. A. McCance, C.B.E., M.D., PH.D., F.R.C.P., F.R.S.; E. M. Widdowson, D.SC. London: H.M. Stationery Office. 1960. Pp. 252. 30*s*.

In 1939 the first edition of these essential food tables was published. Professor McCance and his colleagues had then evolved a system of analysis which could determine the important proximate principles of a diet, including a number of the mineral constituents, but vitamins were not included—a definite gap, but understandable at the time. The analysis in the first edition related to foods in the raw as well as those prepared for table. In 1946 a second edition was published, and since then many new foods have become available and many of the wartime foods in the 1946 edition have disappeared. In the new edition, more than a hundred new foods have been added to the tables, and the figures for many proprietary foods have been adjusted in accordance with changes in manufacturers' formulae.

A welcome addition is the inclusion of new sets of tables giving the vitamin and amino acid contents of foods. For the data on vitamins and some of those on amino acid content, the authors have relied on a comprehensive survey of the literature: the rest of the amino acid analyses are their own work. From all these sources they have derived figures for the main protein foods—cereals, meat, fish, egg, and milk and its products, and for a limited number of nuts and vegetables.

In part 1 the figures for calorific constituents, water, and minerals of individual foods are the result of direct analysis by McCance, Widdowson, and Southgate, those for most of the cooked dishes being obtained by computation from figures for the individual ingredients. The tables are in two main sections giving the composition of each food per 100 g. or per 100 ml. and composition per oz. The note on the calculation of the calorific value of foods and of diets by Miss Widdowson should be read by all using these tables.

In part 2, I. M. Barrett and E. M. Widdowson present the data on vitamin content, and in Part 3, B. P. Hughes deals with the aminoacid composition.

This book now displaces its predecessor as the standard work for all who teach, practise, or research on human nutrition and dietetics, and who will warmly thank Professor McCance and Miss Widdowson for this 1960 edition.

Cancer: the Significance of Delay

Robert Sutherland, M.D., D.P.H., director, British Empire Cancer Campaign (Yorkshire Council) Cancer Survey, senior lecturer in preventive medicine and public health, University of Leeds. London: Butterworth. 1960. Pp. 213. 30*s*.

The subtitle of this book is misleading, since only the last 53 pages are concerned specifically with the effect of delay in reporting symptoms. The book is really a critical survey of the literature on factors which may influence prognosis in cancer. After two short preliminary chapters, the author considers in turn the evidence about the effects of tumour characteristics, host characteristics, and environment. These three chapters occupy about two-thirds of the book, and the material is clearly presented and extremely well documented.

The heart of the matter, however, is in the last chapter. Dr. Sutherland first discusses the statistical evidence. If the mean survival time after treatment, or the proportion of 5-year survivors, is related to the delay between the onset of symptoms and treatment, a common finding is that prognosis apparently deteriorates as the delay lengthens from zero to some critical value, but for longer delays the prognosis apparently improves. If the reasons for delay were entirely independent of the rate of development of the tumour, a useful analysis could be made. Suppose, for example, that one compares two groups of patients with cancer at a particular site: group A with a delay of 0-6 months, and a mean survival of 3·5 years after treatment; and group B, with a delay of 2-2$^1/_2$ years, and a mean survival of 3·0 years. Dr. Sutherland points out that these two survival periods are not comparable, being measured from different starting-points. His own solution is hardly more satisfactory. It is to add the delay period to the survival period; thus, group A would have a mean survival period from onset of symptoms of 3·75 years, compared with 5·25 years for group B. This is misleading because, by definition, group B contains no individuals with a survival of less than 2 years from onset of symptoms. A better procedure would be to compare, in different groups, the mortality-rate *amongst survivors* during comparable periods after the presumed date of onset. One could compare, for instance, the mortality-rate between 3 and 4 years after treatment in group A with the mortality between 1 and 2 years after treatment in group B.

These refinements are, however, of mainly academic interest, for the whole problem is bedevilled by selection. A group of patients with a moderate delay (say, 6 months) is likely to be relatively heavily weighted with fast-growing tumours which cause particular concern to the patients during this period. A group with a long delay (say, 3 years) must be weighted with slow-growing tumours. This type of selection alone may explain the apparent effect of delay, and there are further complicating factors, such as occasional misdiagnosis and uncertainty about the date of first symptoms. In the absence of any clear statistical evidence, then, Dr. Sutherland relies on general principles. His attitude is summed up in this quotation from Kreyberg:

> "A diagnosis as early as possible is of great importance to a certain, yet unknown, number of individual breast carcinoma patients. As we do not beforehand know who will benefit and who will not, a general plea for 'early diagnosis' is fully substantiated, as every individual salvaged is important. We must, however, always have in mind that the benefit is statistically moderate, and we ought to be modest in our claims as to the possibility of materially altering the situation for the breast carcinoma patients by this approach to the problem."

Some light would be thrown on the problem if we had better estimates of the effectiveness of treatment. The statistics of cancer therapy are, unhappily, as controversial as those on delay, but there is at least some hope, here, of obtaining reliable evidence from controlled trials.

The Organisation of Cells and Other Organisms

Laurence Picken. London: Oxford University Press. 1960. Pp. 629. 25*s*.

The reader opening this book might readily mistake its author: the enormous compilation, the evocative and ruminative concern with large biological outlines which are filled-in with research detail, the scope, and even the full-page Chinese proverb at the end are heavily marked with the imprint of Joseph Needham—so much so that it is hard to read it as other than a sequel to *Biochemistry and Morphogenesis*. Here the concern with Needham's original preoccupation, the way in which "properties generate structures", is carried to the sub-cellular level. In a sense it comes just too early—if indeed we are on the edge of a concrete knowledge of the chemistry of self-replication. But it would be large optimism to assume that we are, and this book, while it must necessarily age at a

depressing rate for the author who has put so much work into compiling and organising our present knowledge, is still likely to remain a standard source for a very long time.

The scope is as the title indicates, the " other organisms " being viruses and schizomycetes. In the course of the study the author reviews the chemical morphology of nucleus, cytoplasm, organelles, and the cell surface, and goes on to the extracellular secretion of " repetitive " structures such as fibres, and finally the contribution of cell-properties to development and epigenesis. The argument is perpetually touching tender spots in current research: it is excellently illustrated and documented, and the resemblance to the Needham manner is carried into the style, which is always literate and sometimes eloquent. As with " research " itself, there are no cut-and-dried " conclusions " capable of summary, but the cytologist specially, and biologists in general, will find the author's tone of work-in-progress very congenial, and the summary of the state of their subject invaluable.

Eat Well and Stay Well

ANCEL and MARGARET KEYS. Special British edition adapted by MAGNUS PYKE. London: Hodder & Stoughton. 1960. Pp. 348. 15*s*.

Dr. Pyke has made a number of improvements to the American edition of this book.[1] Table 1, for example, now compares the mortality from ischæmic heart-disease and other causes in 16 countries rather than in the United States alone. A short section has been added dealing with the important sex-differences in the incidence of ischæmic heart-disease. Many of the menus sound more familiar but no less appealing, and the references have a more international flavour.

The authors are concerned throughout with the implications of over-nutrition. They have provided a reasoned, authoritative, and stimulating " educated man's guide " to diet. It has point and purpose for all to whom the cost of food is not the most important factor determining the choice of menu.

Cancer of the Rectum

Editor: CUTHBERT E. DUKES, O.B.E., M.D., F.R.C.S., consulting pathologist, St. Mark's Hospital, London. Edinburgh: E. & S. Livingstone. 1960. Pp. 304. 50*s*.

IT may seem surprising that a whole monograph can be devoted to cancer of the rectum; indeed there is something to be said against thus ascribing to this viscus an identity separate from the large intestine generally—a convention which arises from a quirk of pelvic anatomy in an organ which has no strict anatomical identity. But, accepting this nineteenth-century convention, let it be said that this book is right up to date.

The first three chapters and an appendix are statistical, with Dr. R. A. M. Case driving his cohort analyses and much else more comprehensible to simple proctological minds. These chapters set a high intellectual level which the rest of the work can never quite achieve since the subject matter is too restrictive. The results of surgical treatment are discussed separately in a later chapter where the figures of 5-year survival appear exceptionally good because they do not include all presenting themselves for treatment; these figures have little value therefore for those wishing to make comparisons, but this drawback is fairly acknowledged by the authors. There is no clear statement of the occasion from which anniversaries are dated; moreover, operative deaths are excluded. It is perhaps a pity that the statistical contributor took no part in framing this chapter.

It is a pleasure to read Dr. Cuthbert Dukes discoursing in a personal way on the causation and control of rectal cancer, though surprising that in such a chapter the evidence of inflammatory disorder to which he himself has contributed plays second fiddle to the adenomata, the importance of which as a precancerous lesion is now more doubtful. It was a good idea to include a chapter on other mammals, though in effect this inevitably becomes a catalogue of those species in which intestinal cancer has been observed and reported, with a useful section on animals susceptible to induced tumours and what may induce them.

1. See *Lancet*, 1959, ii, 773.

The rest of the work follows well-known lines of pathology, surgical technique, and postoperative care, with a good chapter on anatomy. There is even the hallmark, now hallowed by time, of so many proctological works—somewhat superfluous illustrations of a proctoscope and a sigmoidoscope. These chapters seem to be written for the tyro, though it will interest the expert to discover that such is the strength of tradition that removal to the coccyx is still being advocated in the technique of rectal excision though this manœuvre is unnecessary and sometimes adds considerably to the patient's discomfort.

Surgical Anatomy of the Bronchovascular Segments

WILLIAM E. BLOOMER, M.D., assistant professor of surgery; AVERILL A. LIEBOW, M.D., John Slade Ely professor of pathology; MILTON R. HALES, M.D., assistant professor of pathology, Yale University School of Medicine. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 273. 132*s*.

THIS book is based on an analysis of the segmental and vascular structures in 50 multicoloured plastic corrosion casts, and provides the first extensive stereoscopic approach to the segmental anatomy of the lung. It is especially designed to serve as a guide to the dissection of the bronchovascular segments, which has been necessitated by the increasing recognition that the bronchovascular segment is the true anatomical, as well as surgicopathological, unit of the lung.

Although peripheral lesions of the lung can be removed by " wedge " resection, the approach to lesions confined to a single segment, deep within a lobe, when conservation of tissue is paramount, demands an accurate knowledge of vascular and bronchial relationship.

The authors present first a general account of the anatomy of the lung, then a detailed analysis of the variations in the bronchi and vessels of each lobe, and lastly a discussion of the problems of surgical approach. The last chapter is devoted to the correlation of their findings with radiological appearances. The nomenclature of Boyden has been used, and in most of the tables the findings of Boyden and his coworkers are listed side by side with those of the present authors, thus giving a detailed comparison of both series. The book is elaborately illustrated with photographs of casts, explanatory diagrams (many of which are in two colours), and radiographs.

This painstaking study, which has been beautifully produced, will be invaluable to anatomists, pathologists, radiologists, and thoracic surgeons.

Disease in Infancy and Childhood (3rd ed. Edinburgh: E. & S. Livingstone. 1960. Pp. 714. 55*s*.).—Four years after the second edition, this comprehensive textbook by Prof. R. W. B. Ellis has been revised to include recent advances. The chapter on communicable diseases has been enlarged to contain more information on viruses such as Coxsackie, Echo, and adeno-viruses, and the recent chromosomal findings in mongols and in Turner's and Klinefelter's syndromes are described. The excellent chapter of 115 pages on congenital malformations is rightly the longest, but cyanotic attacks in Fallot's tetralogy are omitted and the Eisenmenger complex is confusingly described as " a variation of Fallot's tetralogy but without obstruction of the pulmonary circulation ". This excellent book retains its clarity and interest and will continue to be widely read.

The Recovery of Man in Childhood (London: Hodder & Stoughton. 1958. Pp. 211. 21*s*.).—Child psychiatrists and others, faced with a particularly difficult disposal of a child presenting intellectual or behaviour problems, often consider a Rudolf Steiner school. These schools are better known for the love and care which they bestow upon the handicapped than for the theoretical background to their techniques. The author of this book, Mr. A. C. Harwood, has taught in a Steiner school for many years (though one for normal children), and he has written as clear an account of some anthroposophical views on child development as so far exists.

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Commonwealth and Common Health

THAT was the title of Sir ARTHUR PORRITT's thoughtful address to the British Medical Association last year [1]; and in Auckland this week Sir DOUGLAS ROBB has given the thought new urgency with a call to action. Both of them New Zealanders by birth, these successive presidents of the Association have a wider view than most of us, absorbed as we are by our own work. Here is the situation as ROBB sees it:

"All the peoples of the world suddenly seem to have grasped the idea that they need not continue in hunger, poverty, ill-health, and ignorance. They know with Isaiah that every valley can be exalted and every mountain and hill laid low, and they are determined in action to bring about the changes they desire. The newly awakened countries may not know clearly what the good life is, nor how to achieve it—any more perhaps than we do in the wealthier countries. But they do recognise some of the bad features of their present condition, as we do, and they will try to remedy them. They see in technology the way to grow more food, secure more shelter, and gradually to ameliorate their lot. How proper it is for us, who for the moment—perhaps a very fleeting moment—know a little more about these things, to wish to help; how dismal our failure if we sit at ease in our Zions and do nothing. In terms of practical politics and even of self-interest it may be better to lend a hand—where it is wanted—while the brief opportunity is there."

In medicine the opportunity is obvious; yet as a profession we have not yet risen to it.

The new president of the B.M.A. has chosen the psychological moment for his appeal. Many of us are much impressed by the usefulness of schemes by which a few universities and hospitals in Britain are helping medical schools in the tropics, and interchanging staff. We have seen the kind of provisions the Medical Research Council have found necessary for ensuring continuance of their investigations, especially in Africa.[2] We have become aware of the heavy loss sustained by former Colonies when doctors in their service have to return to Britain—a mutual misfortune which the British Government has generously countered by making it financially possible for these doctors to go on with their work, and indeed for others to reinforce them for short periods.[3] We now know pretty clearly what are the factors—particularly in the National Health Service [4]—which so often make the young British doctor seem less adventurous and less altruistic than his forebears. Finally we are coming to recognise that, as ROBB put it, "a man's training for his life's work in the United Kingdom could in almost every instance be greatly enriched by well-chosen periods abroad".

1. *Brit. med. J.* 1960, i, 1907.
2. Medical Research Council: report for 1958-59, p. 7; see *Lancet*, 1960, ii, 193.
3. *Lancet*, 1960, ii, 1013.
4. *ibid.* 1958, ii, 1111.

As one who has seen something of the immense differences of medical service in different parts of the Commonwealth, and the gross inequalities in training, ROBB finds them intolerable. Some sharing is clearly necessary if all areas are to be brought at least to an acceptable minimum: "the contrast between malnutrition and emaciation in one country, as the dominant medical picture, and obesity and vascular degenerations as the besetting sins in a neighbouring one, cannot be harboured for long in a world so full of aeroplanes, radio, and television". In medicine, the aim eventually must be to have free movement, without penalty, throughout the various countries; and to have uniform standards of education for nurses and ancillaries as well as doctors. But there is much to be done before this, and we should lose no more time in starting on what ROBB calls the developmental stage of the task—building on existing efforts, and in their spirit, but nevertheless attempting something much more comprehensive.

The urgent need, as he sees it, is fuller interchange of doctors; and nowadays there is in fact no reason why medical men and women should not move easily from one job to another in the Commonwealth—if only there were an agency which would ensure that air fares were paid, that pay and pension rights were preserved, that conditions of work were satisfactory, and that opportunities at home were not lost. There are many universities and hospitals abroad which could offer them invaluable experience and whose present unattractiveness is due simply to their having a staff which is too small and therefore almost overwhelmed. Could not the mutual arrangements between distant institutions now be greatly multiplied? In ROBB's words, "one could almost think of an association or a club of which hospitals, universities, or even Governments wishing to take part in the scheme could become members". Belonging to the club would bring obligations as well as privileges: member institutions which were short of doctors would have to offer good conditions of work (for which they might need help) while parent institutions in better-developed countries might themselves have to revise their teaching arrangements so as to give the best possible training to doctors working there in exchange.

"Living accommodation at each end should be available so that no delays and frustrations should diminish the great advantages of air travel. It would amount to the provision at both ends of funds and equipment over and above the bare needs (and heaven knows these are bare enough in many countries today) to allow a percentage of staff and trainees to be exchanging abroad. Additional needs would be a central secretariat which, in time, would become a big affair, and a certain capital sum for management and for backing at least in the initial stages."

There is more in the idea, too, than hospitals and

universities. As ROBB said, every kind of medical man and every kind of health operation is wanted:

" I am told that there is a great need for medical men for general duties in various parts of Africa—general practices, simple public health, and sanitation. What better change and challenge could there be to a general practitioner in the United Kingdom or in New Zealand, rather harassed and bowed down by the daily and nightly demands made upon him, than the prospect of a tour of duty, in Uganda or Tanganyika, for say two years ? Even if he found the effort of facing up to the undertaking a great one, I feel sure the general experience, the geography, and the human problems he would encounter could not fail to interest him and enrich his life."

Complementary to Sir DOUGLAS ROBB's address are the more detailed proposals made by Prof. KENNETH HILL,[5] who has given long thought to what might be done. Recognising that a new deal is required if the necessary doctors are to go to the developing countries, both within the Commonwealth and outside it, he puts forward the kind of " code of secondment " which would have to be applied to give them confidence in going overseas. For such a code to be adopted the first necessity is a change of attitude by which a period of overseas service would be recognised as an asset to promotion in the medical services, rather than the reverse. If the public as well as the profession are to see the world in a new and more realistic as well as altruistic light, the call must come first from a high level. The Commonwealth Education Conference, which initiated a scheme for supplying more teachers to developing countries, came out of a meeting of Commonwealth Ministers; and ROBB suggests that the medical scheme might similarly be launched by the Commonwealth Ministers of health and education. Since money will be needed from official as well as unofficial sources, this plan has attractions, provided it does not mean delay. Professor HILL, however, has an alternative plan, which, with its stronger emphasis on the contribution of our profession, may have more appeal to doctors. What we have to do, he says, is to infuse nationally a spirit of service and dedication to Commonwealth development, so that service overseas shall again be " part of the pattern of the national life, as reflected in Medicine ". To this end, he feels " a crusade should be started with its head the ex-president of the B.M.A., the Duke of Edinburgh, and its convener, the present president, with the cooperation of the Presidents of the various Royal colleges ".

The word " crusade " is appropriate in a way, because it denotes both unselfishness and enterprise. Whatever arrangements are made—whatever code is adopted—courage may be needed to uproot onself, and perhaps one's family, to go abroad; and courage can come from the sense of crusading. Nevertheless the scheme now conceived is something more than an emergency measure of help towards developing countries where medical gaps are at present conspicuous. On Sir DOUGLAS ROBB's more " distant view " these countries, both inside and outside the Commonwealth, will eventually have services comparable with our own; but, when this is achieved, we shall still require wide exchange of doctors, especially in the years of postgraduate training. The word crusade is suitable in that what has to be done first is to persuade everybody that people who respond should be honoured for going and cherished on their return. But ROBB was right in emphasising that nowadays whatever is offered abroad must be offered on a basis of mutual respect and equality—with readiness to return as soon as the developing country can manage on its own. He and HILL, evidently agree that, though there is a strong case for starting the new organisation as a responsibility of the Commonwealth, which has alike great needs and great resources, this from the first should certainly not exclude assistance to countries outside.

The name of this new undertaking is far from unimportant to its future. For our part we should like it to have some such simple title as the Commonwealth Medical Society, appropriate to an organ of association and friendship rather than of government. Whatever it is called, it must, as Sir DOUGLAS ROBB says, combine the compassion of medicine with the touch of imagination that enables people to look up from their work and see greater possibilities. If we are now to live in one world, let us make the best of it; and here (as he put it) is " a chance to emphasise the good in contrast to the many opportunities for evil ".

5. *Brit. med. J.* Jan. 14, 1961, p. 117.

Closed-circuit Halothane

SINCE the anæsthetic properties of bromochlorotrifluoroethane (halothane) were discovered by SUCKLING[1] in 1956, the physical and pharmacological characteristics of this substance have been more thoroughly investigated than those of any other anæsthetic agent. Nevertheless its place is still disputed. Some maintain that it transcends all other agents; while others, more conservatively, admit only that it is a useful non-flammable and non-explosive anæsthetic more potent than nitrous oxide or trichloroethylene. Whatever its place in practice, halothane is expensive; and accordingly attention has turned to its administration in a closed circuit with small gas-flows.

The wastage of anæsthetic vapour depends on the fresh-gas flow and the concentration of anæsthetic in the circuit [2]; the higher the flow-rate, the greater the escape of anæsthetic vapour through the expiratory valve to the atmosphere. In a non-rebreathing circuit the concentration of anæsthetic vapour inspired by the patient will be that leaving the vaporiser. Provided this concentration is known, there is no safer method of administering any liquid anæsthetic agent; but it requires high fresh-gas flows, and, with an anæsthetic as costly as halothane, it is most uneconomical. Thus it would be desirable to use halothane in a closed circuit with small flows if this did not add to the risk for the patient. Unfortunately there is still some uncertainty about the concentration of anæsthetic vapour inspired by the patient in such a

1. Suckling, C. W. *Brit. J. Anæsth.* 1957, **29**, 466.
2. Mushin, W. W., Galloon, S. *ibid.* 1960, **32**, 324.

circuit, and many anæsthetists question the safety of using potent anæsthetics with low flows.

MUSHIN, MAPLESON, and GALLOON in Cardiff have analysed the factors affecting the inspired concentration in the closed circuit.[2–4] These are the vaporiser concentration, the fresh-gas flow into the circuit, the ventilation, and the uptake of anæsthetic by the patient; and their influence on the inspired concentration depends on the position of the vaporiser. If the vaporiser is within the path of the patient's ventilation (V.I.C.), which then vaporises the liquid anæsthetic, the ventilation is the most important factor influencing the inspired concentration. This is claimed as an advantage of this system, as the ventilation will fall with high concentrations, leading to less vaporisation and thus providing the so-called "built-in safety factor". MARRETT[5] has emphasised that this applies only if the patient is breathing spontaneously: it is clearly dangerous to apply artificial ventilation to a patient with the vaporiser inside the breathing circuit. Some of the cases of cardiac arrest associated with halothane have undoubtedly arisen where artificial ventilation has been applied with this system.[6–8] When the vaporiser is placed outside the path of the patient's ventilation (V.O.C.), vaporisation of the liquid anæsthetic is not affected by changes in ventilation, and these changes produce only a small effect on the inspired concentration.[3] Artificial ventilation can therefore be instituted with much greater safety in this type of closed circuit. Moreover, reducing the fresh-gas flow also reduces the inspired vapour concentration for a particular tap setting, so the greatest possible economy can be obtained with greater safety than in the V.I.C., where reduction of fresh-gas flow leads to higher inspired concentrations.

Most anæsthetists would agree that knowledge of the concentration of anæsthetic vapour inspired by the patient on the closed circuit would be of great value. With the vaporiser inside the circuit this is rather difficult to estimate, owing to the profound effect of ventilation on the vaporisation of anæsthetic. On the other hand, most of the vaporisers applied outside the circuit have been calibrated or are thermostatically controlled, and with this system ventilation has no effect on vaporisation. The inspired concentration can much more easily be determined, and GALLOON[9] has produced a calculator which provides an approximate estimate of the inspired concentration under various circumstances of fresh-gas flow, ventilation, and tap setting. This should prove a useful guide; but it should not be allowed to replace clinical assessment of the patient's response and behaviour. One of the fears of using halothane in a closed circuit has been that vapour concentration might build up rapidly in the circuit; but in fact this does not occur, and experimental evidence[4] shows that equilibrium will soon be reached between the amount of anæsthetic entering the circuit from the vaporiser and the amount leaving it whether by inhalation or out through the expiratory valve. Clinical experience confirms that, even with very low fresh-gas flows, the circuit concentration will remain steady for fairly long periods—indeed for as long as halothane is extracted from the circuit by inhalation and is deposited in the tissues. That this process goes on for many hours has been shown both in animals[10] and in man,[11] not only with halothane but with other anæsthetic agents.[12 13]

Apparently either type of closed circuit is equally safe in the hands of the experienced anæsthetist. For the inexperienced administrator a completely non-rebreathing circuit with high flows is certainly the safest; and where economy has to be considered, he would be better off with low fresh-gas flows in a closed circuit in which the vaporiser is outside the breathing circuit, particularly if artificial ventilation may be instituted.

The careful series of articles from the Cardiff school has cleared away much of the fog of uncertainty surrounding halothane in closed circuits, and has provided a basis for resolving problems concerning the use of other volatile anæsthetics in closed circuits.

Thiacetazone and Isoniazid

THIACETAZONE has been resurrected. Its use in tuberculosis was first reported in 1946 from Germany[14]; but in this country it was tried on only a small scale. The reported high risk of toxic effects[15] prevented its being fully studied in Great Britain and the U.S.A., and after about 1950 little thought was given to it. No extensive controlled investigations were carried out, and the early clinical studies were not planned in such a way that its therapeutic effects alone or with other drugs could be accurately assessed. In some other countries the thiosemicarbasones were, however, not forgotten entirely, and claims were made that a proprietary mixture of isoniazid and a low dose of nicotinaldehyde-thiosemicarbasone was effective, with little toxicity and some delay in the emergence of resistant strains.[16–19] The evidence for the claims was not fully satisfactory, and only one of these studies[19] was a comparative trial.

In 1957 the Tuberculosis Research Unit of the Medical Research Council, in its search for a satisfactory substitute for *p*-aminosalicylic acid (P.A.S.), the disadvantages of which are well known, began in East Africa a small pilot study of thiacetazone (*p*-acetamido-benzaldehyde thiosemicarbasone) given with isoniazid. The bacteriological results were encouraging. It seemed, however, that the dosage tried—200 mg. a day—might be too toxic for general use. A larger, con-

3. Mapleson, W. W. *ibid*, p. 298.
4. Galloon, S. *ibid*, p. 310.
5. Marrett, H. R. *Anæsthesia*, 1959, **14**, 28.
6. Foster, C. A. *Lancet*, 1957, i, 1144.
7. Stephen, C. R., Lawrence, J. H., Fabian, L. W., Bourgeois-Gavardin, M., Dent, S., Grosskreutz, D. C. *Anesthesiology*, 1958, **19**, 197.
8. Chang, J., Macartney, H. H., Graves, H. B. *Canad. anæsth. Soc. J.* 1957, **4**, 187.
9. Galloon, S. *Anæsthesia*, 1961, **16**, 96.
10. Duncan, W. A. M., Raventos, J. *Brit. J. Anæsth.* 1959, **31**, 302.
11. Mapleson, W. W. Personal communication.
12. Haggard, H. W. *J. biol. Chem.* 1924, **59**, 737.
13. Severinghaus, J. W. *J. clin. Invest.* 1954, **33**, 1183.
14. Domagk, G., Behnisch, R., Meitzsch, F., Schmidt, H. *Naturwissenschaften*, 1946, **33**, 315.
15. Hinshaw, H. C., McDermott, W. *Amer. Rev. Tuberc.* 1950, **61**, 145.
16. Kossmasm, F. *TuberkArzt*, 1954, **8**, 479.
17. Lunger, C. *Wien. klin. Wschr.* 1954, **66**, 440.
18. Tuczek, H., Saupe, M. *Münch. med. Wschr.* 1954, **96**, 858.
19. Jancik, E. *Rozhl. Tuberk.* 1960, **20**, 169.

trolled trial was started, with 150 mg. a day.[20] It followed the well-established pattern of strictly controlled comparative investigations that have given valuable information over the past fifteen years in this country and elsewhere, and was carried out with all the thoroughness that has characterised the work of this research unit. Eight hospitals and laboratories in Uganda, Kenya, and Tanganyika cooperated; the investigation was coordinated in East Africa by the Department of Medicine, Makerere College, Kampala, and in London by the Tuberculosis Research Unit. Two other M.R.C. units took part—the Unit for Research on Drug Sensitivity in Tuberculosis and the Statistical Research Unit.

156 patients with acute extensive pulmonary tuberculosis were allocated at random to treatment groups. (One group received the substituted thiourea, SU1906, with isoniazid; the results were soon found to be unsatisfactory.) One group received isoniazid 100 mg. twice daily with 5 g. of the sodium salt of P.A.S. twice daily; another group the same dose of isoniazid with thiacetazone 75 mg. twice daily. Treatment was given to the patients as inpatients for six months and as outpatients for a further six months. By the end of a year, of those with initially sensitive cultures treated, 88% in the group treated with isoniazid and P.A.S., and 87% in the group treated with isoniazid and thiacetazone, had negative cultures. From a detailed analysis of the clinical, radiographic, and bacteriological results it was concluded that 150 mg. thiacetazone daily in two equal doses was of similar efficacy to sodium P.A.S. in two doses of 5 g. daily when given with isoniazid.

Many toxic manifestations have been attributed to the thiosemicarbasones: hæmolytic anæmia, granulocytopenia, purpura, nephritis, cerebral œdema, liver damage, and hypersensitivity reactions, including the Stevens-Johnson syndrome.[21] In the East African investigation toxic reactions occurred in 4 of 51 patients receiving thiacetazone and isoniazid (2 neutropenia, 1 hypersensitivity reaction, 1 intractable vomiting); treatment had to be changed in all 4. But there were also toxic reactions in 2 of the 50 receiving P.A.S. and isoniazid; both had liver damage, and 1 died from it. Thus, on the basis of this experience, it seems likely that two doses of 75 mg. of thiacetazone daily is not too toxic to be an acceptable treatment. It has the advantage of being relatively cheap, so that tablets containing both isoniazid and thiacetazone could be both cheaper than cachets of sodium P.A.S. and isoniazid and possibly more acceptable to patients. But the report rightly emphasises the need for caution before introducing this combination for routine use, particularly in outpatients. It is very important that the results of this preliminary study should not be misinterpreted. Further extensive investigations are necessary before thiacetazone and P.A.S. can be accepted as a substitute for the well-tried regimen of P.A.S. and isoniazid.

The finding that thiacetazone may possibly be a satisfactory substitute for P.A.S. is of considerable importance. Largely because of the expense of P.A.S., isoniazid has been recommended, and widely used, alone. A controlled trial in East Africa showed that the results obtained with it in patients treated in hospital were inferior to those with P.A.S. and isoniazid.[22 23] The dose of isoniazid was 100 mg. twice daily in one group and 400–600 mg. twice daily in another. In a similar trial by the Tuberculosis Chemotherapy Centre in Madras [24] three isoniazid regimens were employed: 100 mg. twice daily, 200 mg. twice daily, and 400 mg. once daily (for patients weighing 100 lb.). They were compared with 5 g. sodium P.A.S. and 100 mg. isoniazid twice daily, and the patients were all treated at home. Again, all isoniazid regimens proved less effective. The single daily dose of isoniazid was the most effective, but even with this 27% were judged to have unsatisfactory responses at the end of twelve months, compared with only 8% of those who took P.A.S. with isoniazid. In both the East African and Madras studies the higher doses of isoniazid were associated with an important incidence of peripheral neuritis. The incidence can be reduced by giving pyridoxine at the same time, but this adds considerably to the expense. There is a suggestion that vitamin-B complex, which is cheaper, might also be effective,[25] but both add to the cost of treatment without increasing its efficacy.

The resurrection of thiacetazone suggests several profitable lines of inquiry. Besides finding out the minimum effective dose in combination with low doses of isoniazid, it would be worth while investigating the efficacy of single daily doses of both drugs and of combinations of P.A.S., isoniazid, and thiacetazone. This triple-drug regimen could be compared with streptomycin, P.A.S., and isoniazid, which is now generally recognised as the most effective combination, though it is by no means generally applicable. P.A.S. and isoniazid together give only about 90% success in acute extensive disease, and even a 5% increase with the addition of an oral preparation would be a worth-while improvement. As we have said before,[23] there is scope for investigating regimens that take account of the stage of treatment as well as of the extent of the disease. The Tuberculosis Chemotherapy Centre in Madras compared a year's isoniazid and P.A.S. followed by isoniazid alone for a further year with a year's isoniazid and P.A.S. and no chemotherapy in the second year.[26] The results suggested that, in the circumstances of this investigation, the second year's isoniazid treatment did not reduce the frequency of bacteriological relapse while it was being given. Judged by criteria far more strict than are usual in chest clinics, 3 (5%) of the 65 patients who received isoniazid in the second year had more than one positive culture during the year, compared with 5 (8%) of 61 who received an inert preparation. Another regimen to be

20. East African/British Medical Research Council Thioacetazone/Diphenylthiourea Investigation, *Tubercle, Lond.* 1960, **41**, 399.
21. Moore, W. *ibid.* p. 448.
22. East African/British Medical Research Council Isoniazid Investigation, *ibid.* p. 83.
23. *Lancet*, 1960, i, 1013.
24. Tuberculosis Chemotherapy Centre, Madras. *Bull. Wld Hlth Org.* 1960, **23**, 535.
25. Devadatta, S., Gangadharam, P. R. J., Andrews, R. H., Fox, W., Ramerkrishnan, C. V., Selkon, J. B., Velu, S. *ibid.* p. 587.
26. Velu, S., Andrews, R. H., Devadatta, S., Fox, W., Radhakrishna, S., Ramakrishnan, C. V., Selkon, J. B., Samasundaram, P. R., Subbaiah, T. V. *ibid.* p. 511.

tried could be streptomycin, P.A.S., and isoniazid, followed, when the sputum becomes bacteriologically negative, by isoniazid alone or isoniazid with thiacetazone. Such a trial would require large numbers of patients, and probably only an international body, such as the International Union Against Tuberculosis, could carry it out.

Annotations

PAYING FOR THE N.H.S.

THE Minister of Health's proposals for new charges to help meet the cost of the National Health Service (see p. 345) seem to have three main purposes. The first is to transfer some of the burden from the Exchequer to the healthy insured population: increases in contributions to the N.H.S. by up to 1*s.* (including 2*d.* contributed by the employer) are expected to yield some £49 million in a full year. The other two purposes are to transfer a further small part of the cost to the patient himself, and to inhibit extravagance. Thus the charges for amenity beds are to be raised, the proportion of the cost of spectacles and dentures payable by the patient is to be increased, welfare foods are to be sold at cost price, and the prescription charge, at present 1*s.*, is to be raised to 2*s.*, per item.

Of these charges, however disagreeable, only two are likely to reduce seriously the public's use of the service—namely, those for welfare foods and for prescriptions. The prescription charge is especially objectionable because for the ailing this is liable to be a severe recurrent toll on low incomes. Moreover as a weapon against the mounting cost of the pharmaceutical service, such a charge is not only blunt but wrongly aimed. If indeed the drug bill is too high the Minister should turn, not to the patient (who after all cannot obtain drugs at will under the N.H.S.), but to the prescriber and possibly to the manufacturer. It is quite wrong that the majority of patients who use the pharmaceutical service responsibly should suffer for the excesses of an overpersuasive few. Moreover, though the cost of this service has admittedly increased, there is no denying that more effective pharmaceutical preparations have helped to shorten illness, lessen ill health, and decrease the call on hospitals.

The question is: By how much? This question cannot be answered, any more than we can tell how long the nation would obtain a good return by setting aside increasing amounts for the N.H.S. Thus, for lack of a reliable balance-sheet (which no service can have) the N.H.S. is recurrently exposed to political whim. What is clear is that, judged by the proportion of the national income devoted (either personally or centrally) to health services, we are spending no more than other countries; and the present increase in the estimates, on which the Minister had laid some emphasis, is largely due to a capital-investment programme deferred from earlier years when the proportion spent on our health services fell below that in other countries.

Even without the latest increase in estimates, the Minister's proposals (which are being discussed by the House of Commons as we go to press) might have been little different, for they seem to rest on a conviction that the taxpayer's contribution should be lessened. The proposed charges, insofar as they may occasionally cause hardship and even deter a few from necessary use of the service, are damaging and retrogressive.

SURGEON AND ENGINEER

MECHANICAL devices and engineering techniques have made possible many of the impressive surgical advances of the past decade. Machines now take over vital functions during surgical operations, and many less obtrusive instruments have been successfully designed to enhance the surgeon's skill. The complex and often lengthy operations of today threaten to tax the limited resources of surgery so that its benefits may be denied to some; but, by providing instruments that bring an element of automation to surgical technique, engineering skill can save time and relieve the surgeon of the drudgery of repetitive movements. For example, in any operation much time is spent ligating blood-vessels and stitching tissues; and a hæmostat which automatically ligates the vessel it picks up has already been evolved in Germany, and has been adopted by many European surgeons. Greatly improved "hæmostatic machines" for vessels unsuitable for diathermy coagulation could be designed. At least one centre in this country is considering methods of welding plastics within a surgical field for hæmostasis and tissue union. The semiautomatic needleholder represents a step towards the use of a simple machine to reduce repetitive movement by the surgeon. Elaborations of this device could, doubtless, take over the complete sequence of actions necessary to pass a needle and, moreover, could have some form of power drive. But the evolution of machines that are to be so intimately harnessed to the surgeon-craftsman is inevitably slow: attempts to advance too rapidly with designs possibly short of perfection can only convince the majority of surgeons that mechanical aids are impracticable.

Astonishing though the developments in surgical engineering have been over the past decade, the critical observer may wonder uneasily whether we in Britain have progressed as far and as fast as might be expected. Are our surgical manufacturing firms being given adequate new ideas to compete with their American and European counterparts? Is our approach too haphazard, casual, or even conservative? At the moment no adequate national organisation ensures that British surgical technology is second to none. In Moscow the Scientific Research Institute of Experimental Surgical Apparatus and Tools, within the Sklifosovsky Institute, has produced impressive results by providing the surgeon with expert engineering advice and assistance. In Britain notable individual contributions have been made; the surgical firms have been eager to help with promising ideas, and several new allies of surgery have appeared among mechanical and electronic engineering firms. The increasing sponsoring of medical inventions by the National Research Development Corporation (N.R.D.C.) is encouraging, but there still seems a need for a body of surgeons and engineers who could cooperate on the problems of surgical technology. Such a body could form a panel of experts to whom the individual inventor could appeal for assistance so that promising ideas need not be neglected for lack of engineering skill or of financial support. The engineer cannot know the needs of the surgeon, any more than the surgeon can know of the many devices and specialised technical knowledge (often in fields apparently far removed from surgery) that the engineer can offer him. The initiative,

however, must come from surgeons who are far-sighted enough to appreciate the full resources of present-day mechanical engineering, metallurgy, and electronics.

The suggested body might be linked with several existing organisations, including the Royal Colleges of Surgeons, the Medical Research Council, and possibly the Department of Industrial and Scientific Research. The N.R.D.C. is of great value, overcoming the ethical difficulties of protecting British medical inventions by patent cover; but new ideas must come from elsewhere. Perhaps, too, one of the large philanthropic foundations would sponsor a department of surgical engineering and technology.

Closer alliance between surgery and engineering, however achieved, could not fail to benefit both surgeon and patient.

URINARY OSMOLALITY AFTER OPERATION

MEASUREMENT of the concentration of the urine is generally believed to be a good way of distinguishing between the oliguria due to water lack and that due to renal tubular necrosis.[1] Oliguria is common after severe accidental injury and many major surgical operations, but the precise significance of this kind of oliguria in relation to water intake and renal function has not been defined. Raisz and his associates [2 3] have now reported studies of the effects of water deprivation in healthy young men, in patients without renal disease, and in patients submitted to major surgical operations.

So many factors, such as previous variations in protein and water intake, changes in the amounts of solutes other than protein requiring excretion, and changes in renal blood-flow, can affect urine volume and concentration that precise definition of the conditions of any experimental observation on urine osmolality is essential. Raisz et al. deprived their subjects of fluid for twenty-four hours from midday but allowed them a dry supper containing at least half a pound of meat or cheese. Longer dietary stability and more complete starvation for food as well as for water, though possibly not affecting the results, would have enabled these to be compared more confidently with those of similar experiments.

The mean maximum urine osmolality in healthy young men was 1189 mOsm. per kg. body-weight (range 967–1342 mOsm.), which was rather higher than could be expected for male hospital patients of the same age with good renal function. Raisz et al. recognise that previous restriction of protein intake or disturbances of fluid and electrolyte balance may have a bearing on the lower renal concentrating capacity of their patients. They also studied 50 hospital patients, 20 of whom had peptic ulcer. The mean maximum urine osmolality of the hospital patients was 942 mOsm. per kg. (range 661–1262 mOsm.) and there were significant decreases in both osmolality and creatinine clearance with increasing age.

In 14 patients the effects of operation were compared with those of simple water restriction several days before operation and again in 4 patients two or three weeks after operation and in 2 others nine months after operation. Vasopressin was administered with the 5% dextrose solution which was given by intravenous infusion during the operation in quantities that were never less than 100 and in some cases were as much as 800 milliunits per hour. Two units of vasopressin was also administered two-hourly on four occasions on the first postoperative day. The volume and type of fluid administered by intravenous infusion after operation varied widely, but in all patients except 1 exceeded the loss of fluid as urine or by gastric aspiration by 1205–3375 ml.

The urine collected during operation showed a distinct decrease in osmolality and creatinine clearance, which was unaffected by the administration of vasopressin. The close relation of decreases in creatinine clearance and of concentrating capacity suggests that the deficient concentration may be related to changes in glomerular filtration. In most subjects the sodium concentration fell in the small volumes of urine collected during operation, but the dose of vasopressin was unrelated to the concentration, volume, or sodium content of the urine. This notable reduction in urinary concentrating capacity was transient; and despite the administration of large quantities of water the concentration of the urine increased as the creatinine clearance and solute excretion rose in the early postoperative period, but it did not reach preoperative values until more than twenty-four hours after operation. On the first postoperative day a vasopressin concentration test showed that most of the subjects could produce a urine which, while not as concentrated as that in the preoperative period of water deprivation, was of an osmolality greater than 600 mOsm. per kg. This partial inadequacy after operation may have been due to the large volumes of fluid infused which caused reductions in the osmolality and sodium concentration of the serum; even when vasopressin is given to overhydrated patients the kidneys cannot achieve their maximal concentrating capacity.[4 5]

Measurement of renal concentrating capacity, though not difficult, is of uncertain value in deciding the possible significance of oliguria. Gullick and Raisz [3] suggest that preoperative values of more than 600 mOsm. per kg. appear to indicate good concentrating capacity, but this is not entirely supported by their two cases with the largest falls in creatinine clearance after operation. What is perhaps more important is that oliguria with a low osmolality does not necessarily denote a severe renal lesion such as tubular necrosis, especially in the immediate postoperative period. These papers are chiefly of value in emphasising the fall in urine osmolality which accompanies and follows surgical operations and intravenous infusion of abundant fluid. It would be interesting to know whether this occurs also when the intake of fluid is stopped.

AIR-CONDITIONING MECHANISM OF THE NOSE

AN ingenious technique for studying the air-conditioning mechanism of the nose has been described by Negus.[6] The apparatus delivers to both nostrils an unrestricted supply of air, the temperature and humidity of which can be accurately varied between wide extremes. A manometer connected to an oral tube makes a continuous recording of the nasopharyngeal air pressure, which swings to and fro with respiration. The extent of this swing is inversely related to the patency of the nasal cavities, and therefore gives a measure of vasomotor changes in the nasal mucous membranes. Negus records observations on the warming and humidification of in-

1. Swann, R. C., Merrill, J. P. *Medicine*, 1953, **32**, 215.
2. Lindeman, R. D., van Buren, H. C., Raisz, L. G. *New Engl. J. Med.* 1960, **262**, 1306.
3. Gullick, H. D., Raisz, L. G. *ibid.* p. 1309.
4. Miles, B. E., Paton, A., de Wardener, H. E. *Brit. med. J.* 1954, ii, 901.
5. Epstein, F. H., Kleeman, C. R., Hendrikx, A. *J. clin. Invest.* 1957, **36**, 629.
6. Negus, V. *Ann. R. Coll. Surg. Engl.* 1960 **27**, 171.

spired air in different climatic conditions, and on the effects of nasal obstruction and mouth-breathing. This technique may prove applicable to the study of clinical disorders such as vasomotor rhinitis, and to the evaluation of drugs for the relief of nasal congestion.

THE ASCHOFF BODY

THE β-hæmolytic streptococcus is now widely held to be the primary cause of rheumatic fever. But the rarity with which this organism can be isolated from the affected joints or heart has persuaded most students of this disease that the specific lesions result not from direct microbial action but from some form of hypersensitivity or auto-immunity. Evidence strongly supporting such a hypothesis was described by Murphy and Swift,[1] who had found that rheumatic-like cardiac lesions could be obtained in a small proportion of rabbits subjected to repeated focal skin infections with group-A streptococci. Owing to the type-specificity of antibacterial immunity to streptococcal infections, an essential feature of Murphy and Swift's experiments was the successive use of streptococci of different types to maintain the long-continued state of infection apparently needed to produce rheumatic sequelæ.

The myocardial lesions obtained in these experiments closely resembled Aschoff bodies, which are generally regarded as pathognomonic of rheumatic fever in man. But histological examination of the hearts of affected rabbits shows that the so-called Aschoff bodies are the result of focal muscle-cell necrosis, whereas Aschoff [2] was convinced that in man injury to the myocardial fibres played no part in the formation of the Aschoff body. This is still regarded by most pathologists as a reaction of the specialised myocardial histiocytes to damaged interstitial tissue. Murphy himself is aware of the muscular origin of the focal lesions in his laboratory animals; but he does not regard this as in any way invalidating his original view as to their " rheumatic " nature, since he is convinced that the accepted view of the Aschoff body is wrong, and that it too is the result of focal muscle-cell injury. That such foci of damaged muscle are occasionally seen in rheumatic hearts is not in question.[3] What is at issue between Murphy and his critics is whether such myocardial lesions are true Aschoff bodies pathognomonic of rheumatic fever. The presence of typical Aschoff bodies in the epicardium and in the heart-valves [4]—that is, in situations usually regarded as free from muscle-fibres—seems to refute the contention that the injured muscle-fibres are an essential feature of the Aschoff body. Nevertheless, Murphy,[5] in what must surely be one of the most beautifully illustrated pathological reports ever published, has demonstrated not only smooth-muscle fibres but also striated myocardial fibres both in the epicardium and in the mitral valve as an extension from the left auricle. Ehrlich,[6] however, has drawn attention to Aschoff bodies both within the core of the mitral cusps and in the semilunar valves—sites in which neither variety of muscle-fibre is known to occur. A further objection raised by Ehrlich is the invariable absence of lipofuscin granules from the Aschoff cells. Since this pigment is almost always present in cardiac-muscle fibres, and since it is remarkably resistant to destruction (as is witnessed by its persistence in the phagocytes in the vicinity of myocardial infarcts), its absence from the cells of the Aschoff body is a serious challenge to the myogenic theory. Similar criticisms have been made by Wagner,[7] who points to histochemical differences between Aschoff cells and muscle-fibres. Indeed the presence of acid phosphatase and esterase in Aschoff cells indicates a closer relation to histiocytes than to muscle-fibres—a conclusion supported by the similarity of the nuclear morphology peculiar to these two types of cell.

No-one studying the illustrations in Murphy's latest paper can doubt the occurrence in rheumatic heart-disease of focal lesions of the heart-muscle and of endocardial smooth-muscle fibres closely resembling, if not identical with, typical Aschoff bodies. If, as Murphy maintains, all Aschoff bodies result from focal myocardial damage, this will largely account for the hitherto unexplained development of cardiac failure in acute rheumatic fever. (The absence of histological evidence of muscle-cell damage has till now been a baffling problem.) This feature above all should make Murphy's interpretation acceptable to clinicians if not to histologists. The demonstration of muscle protein in the typical cells of the Aschoff body by means, for example, of a specific fluorescent antibody could go a long way towards convincing the still sceptical pathologists.

DOCTOR IN THE FACTORY

THE Minister of Labour and National Service has expressed the hope that more employers will introduce a medical service into their factories. A booklet prepared by his Ministry and the Central Office of Information [8] describes the medical services in fourteen firms varying in size from 250 to over 5000 employees.

The larger units have full-time industrial medical officers, a number of nurses, and ancillary services such as chiropody, physiotherapy, and dental and X-ray facilities; while in the smaller units the service is limited to a visit from a general practitioner for an hour or two a week. In each firm the employer was asked to give his opinion of the service, and one or two representatives of labour were also asked to comment. Invariably the attitude was of strong approval, and this probably reflects the general view of industrialists with experience of such a service: it is very rare for a firm with an established medical service to give it up. Why, then, do so few firms, especially among the smaller undertakings, have a service of this sort? The most startling revelation to come from the Ministry of Labour Survey in Halifax [9] was that medicine and industry in that town (and there is no reason to suppose that it is exceptional) have almost completely failed to get together on the factory floor. In 200 factories there, each employing over 50 people (more than 22,000 in the aggregate), there were only four part-time doctors, who between them spent a mere fifteen hours a week on this work.

Industry is commonly believed to eschew medical influence in factories on the ground of cost. Yet in these fourteen factories the cost varies from about ninepence per head per week to about double this figure. A farthing

1. Murphy, G. E., Swift, H. F. *J. exp. Med.* 1949, **89**, 687.
2. Aschoff, L. *Verhandl. dtsch. path. Ges.* 1904, **2**, 46.
3. Wagner, B. M., Tedeschi, C. G. *Arch. Path.* 1955, **60**, 423.
4. Ruebner, B. *J. Path. Bact.* 1954, **68**, 101.
5. Murphy, G. E. *Medicine*, 1960, **39**, 289.
6. Ehrlich, J. C. *Ann. N.Y. Acad. Sci.* 1960, **84**, 1006.
7. Wagner, B. M. *ibid.* p. 992.
8. Health at Work: a description of medical services in fourteen British factories. Distributed to factory occupiers; not on sale.
9. Ministry of Labour and National Service. Industrial Health: a survey in Halifax. Report by H.M. Factory Inspectorate and recommendations of the Industrial Health Advisory Committee. H.M. Stationery Office, 1958. See *Lancet*, 1958, i, 679.

per working hour can surely not be regarded as an excessive expense: many firms subsidise their workers' lunch by a shilling or more daily or pay three shillings a week for the maintenance of a worker's overall. Either medicine has singularly failed to sell what it can offer industry or there is not much substance in its claim to partnership in efficient production. One handicap under which industrial medicine labours is that it does not lend itself to estimates of financial profit. Figures claiming to prove that a firm has gained financially by employing a doctor do not bear close analysis; if an employer is to engage one he must do so partly as an act of faith—faith that medical advice and treatment on the factory floor really does contribute to safer and healthier working methods and hence to productive efficiency. The reasons given by employers for their attitude (they are the converted) in this booklet are that time is saved in the treatment of minor accidents and illness, that a pre-employment medical examination safeguards all parties, that medical advice on working conditions is appreciated, and that relations of management with staff are often improved by a medical service. One is left with the conviction that there is more to it somewhere, but this intangible grace is very hard to delineate.

TREATMENT OF LYMPHOSARCOMA

IN 1958 a group of workers at the Memorial Center for Cancer and Allied Diseases, New York, made a plea for surgical treatment of lymphosarcoma in childhood where the disease is localised to one group of lymph-nodes, to bone, or to small intestine.[1] Long survival ensued occasionally, and rather less long survival in about 15% of cases.[2] The same team has now analysed [3] the results of various forms of therapy—either single or combined—in 1269 patients of all ages treated at the hospital in the years 1928–52.

As in the children, the term lymphosarcoma is used to cover giant-follicle lymphosarcoma, reticulum-cell sarcoma, and small-cell lymphosarcoma. Leukæmia and Hodgkin's disease are excluded, although the difficulty of excluding the former with certainty is recognised. In 97 lymphosarcoma patients who presented initially without leukæmic changes, transition to a leukæmic phase took place. The age of these 1269 patients ranged from 22 months to 92 years, the greatest number by ten-year age-groups being in the fifth decade. The overall male-to-female ratio was 1·7 to 1; this ratio was greatest (4·5 to 1) at 11–15 years, and at the extremes of age it approached unity.

Realising how difficult it is to compare the results of different forms of treatment in a chronic disease which has a highly varied natural history and for which there is no sure cure, the New York workers compared the results obtained with the five agents most commonly used in the period under review—namely, radiation, alkylating agents, antimetabolic drugs, adrenal steroids, and radioactive phosphorus. Their criteria of response were not exacting. Complete response denoted complete freedom from grossly detectable disease for a month; partial response denoted objective regression, lasting for at least a week, without concomitant spread of disease elsewhere. They conclude that survival has not improved since 1928, despite all the new forms or new combinations of therapy. They also believe that radiation alone can provide as good results, measured by survival, as any of the new agents introduced since 1940. Surgical procedures were sometimes attempted, usually for early, localised disease. Compared with survival after other forms of treatment, notably radiation, in cases at about the same stage, surgery gave less favourable results; but of 19 patients treated by radical neck dissection, sometimes followed by postoperative radiation, 4 survived for long periods without recurrence.

Some interesting facts about the course of the disease emerged. In children it could be held for a while, but when out of control it was more rapidly fatal than in adults. Females did rather better than males at all ages; and patients with localised disease at the time of the first visit usually survived longer, as did those patients diagnosed as having giant follicular lymphoma. In pre-radiation days, lymphosarcoma was regarded as a distressing and rapidly fatal untreatable disease, tending to affect younger age-groups. Radiation has given most patients with this disease some reprieve.

1. Rosenberg, S. A., Diamond, H. D., Dargeon, M. D., Craver, L. F. *New. Engl. J. Med.* 1958, **259**, 505.
2. *Lancet*, 1958, ii, 950.
3. Rosenberg, S. A., Diamond, H. D., Craver, L. F. *Ann. intern. Med.* 1960, **53**, 877.

CLINICIANS' SALARIES AT CAMBRIDGE

THE University of Cambridge, most of whose ceremonies take place in "the decent obscurity of the Latin tongue", has been arguing about its own salary structure, not only in English but in public. Last week 53% of the members of the Regent House voted by 5 to 3 in favour of their General Board's reports on stipends after, we presume, reading some 44 pages of reports, 22 pages of discussion of reports, and no less than 14 flysheets (arguments and opinions signed by one or more members of the Regent House), whose regular appearance in the morning post has been a feature of Cambridge life since last October.

Although a number of questions was submitted to ballot, the main argument was whether medical staff should be paid more than non-medical, and, if so, whether clinical staff only or preclinical staff as well. The main case against such differentials, which were introduced in Cambridge only in 1949, and then with reluctance, was that the whole staff should be treated the same. But the glaring inequalities in other aspects of the Cambridge scene (especially the differences between being a fellow of a college and not being one) reduce the power of this argument; indeed, these inequalities are at present being investigated by a specially appointed syndicate.

There were two main arguments in favour of differentials. The first—that medical staff could earn much higher salaries outside the university—seemed largely irrelevant as it applied to almost all the scientific staff as well; but, since the holders of clinical chairs are debarred from receiving fees for private practice, these being the natural counterpart of the scientists' fees for industrial consulting, some suggestions were made that differentials might be based on this restriction. The second was that recruiting to the medical departments in general would suffer and that the effect on the new postgraduate medical school would be especially serious.

Those who voted in favour of equality of stipends therefore believe that the advantages of life in Cambridge will tempt the right man to accept a lower salary than he could earn in any other British university, including Oxford.

Special Articles

WHY DOES ANYBODY USE THYROID *B.P.*?

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REGIUS PROFESSOR OF MATERIA MEDICA AND THERAPEUTICS IN THE UNIVERSITY OF ABERDEEN

IT is an axiom of therapeutics that we should use, where possible, specific and pure therapeutic remedies rather than those which have an unknown, inconstant, and unstable content of the therapeutic agent.

The original observations of Gull in 1874 led to the very dramatic results achieved by Murray in 1891 by the subcutaneous injection of thyroid extract in the treatment of myxœdema. In 1892 Fox and Mackenzie in this country, and William Jackson in Boston, Mass. (Jackson 1926), showed the efficacy of thyroid by mouth. Since then countless patients have benefited from thyroid therapy, the value of which lies in its content of thyroglobulin from which the naturally occurring hormones thyroxine and triiodothyronine are derived.

In 1927 Harington and Barger successfully synthesised thyroxine, and this was shown to be metabolically effective in human myxœdema by Murray Lyon (1927). One of the patients upon whom these original trials of racemic thyroxine were conducted died in 1960 in an old folks' home in Edinburgh, at the age of 95, having been regularly maintained since 1926 on a daily dose of thyroid *B.P.*, ultimately only gr. $^1/_4$ daily.

After thyroxine was synthesised it was only used intermittently in clinical therapeutics, but the racemic compound was included in the *British Pharmacopœia 1932*. But its absorption was inconstant, it was very expensive, and it never achieved clinical recognition as a therapeutic tool. It was not included in the *B.P. 1948*.

In 1949, however, a commercially feasible process was developed for synthesising l-thyroxine sodium at an economic price (Borrows et al. 1949, Chalmers et al. 1949). Hart and Maclagan (1950) showed that *l*-thyroxine sodium (hereafter referred to simply as thyroxine) was rapidly and constantly effective when given by mouth, and their results have been confirmed by innumerable other workers. Thyroxine tablets were included in the *British Pharmacopœia 1958* and have been in the *British National Formulary* since 1957. Most endocrinologists, many physicians, and an appreciable number of general practitioners have used thyroxine in preference to thyroid *B.P.* for many years.

Nevertheless, considerable prejudice remains against the use of thyroxine, and most doctors do not use it, in the mistaken belief that it has no advantages over thyroid *B.P.* and that it is much more expensive.

Even quite recently, statements such as "The preparation of choice is thyroid *B.P.*... Thyroxine, the newer and purer synthetic preparation, is expensive, is sometimes procured with difficulty from the chemist, and has no great advantages over the older remedy" (*Scottish Medical Journal* 1957) have appeared (unsigned). *The Lancet* (1958), commenting on the contents of the *British Pharmacopœia 1958*, referred to "thyroxine sodium, a research tool rather than a necessary alternative to thyroid *B.P.* in clinical practice". Wilson and Schild (1959) even state: "Dried thyroid (thyroid *B.P.*) when given by mouth is more readily absorbed than thyroxine. Since thyroxine is so much more expensive than dried thyroid, the latter substance is likely to remain in general use and, as it is an extremely potent drug, its standardisation is of importance."

Misleading and erroneous statements such as these reflect the opinion of many medical men, and in the United States, where thyroxine is less extensively marketed, similar but more emphatic views are predominant.

I here review briefly some of the evidence which suggests that it should no longer be acceptable to use thyroid *B.P.* when a better alternative is available in thyroxine.

THE CASE AGAINST THYROID B.P.

Very large quantities of thyroid *B.P.* are prescribed and dispensed, and we must accept that much of this is taken by patients with obesity, as a tonic, or for ill-defined states not associated with confirmed hypothyroidism. As they are not hypothyroid, small doses of exogenous thyroid merely suppress and replace the patients' endogenous production, leaving their symptoms unaltered. Accurate preliminary diagnostic measures are essential before embarking on a course of treatment which, once started, should be continued throughout the patient's life.

Most thyroid, however, is taken by patients with hypothyroidism of various degrees. Many physicians encounter patients who do not respond as effectively as before to their thyroid medication. Their dose requirement may appear to increase, or they may relapse into frank hypothyroidism while continuing to take their thyroid tablets. Although this is a fairly common experience, it is seldom fully recorded, because all too frequently the facile explanation is accepted that the patient has not taken the tablets, or that the tablets have "gone off". A supply of tablets from a fresh source, and supervised administration of them usually restores normality.

Nevertheless, the reasons for the situation developing are worthy of exploration and explanation, and, among others, Owren (1951), Jackson (1957), Asher (1960), Murray (1960), and Wayne (1960) have commented on the apparent unreliability of thyroid tablets. Episodes of this type increased during the winter of 1957–58 in the endocrine clinic of Edinburgh Royal Infirmary, and although previously we had merely transferred to thyroxine therapy any hypothyroid patient taking thyroid

7 CASES TREATED WITH THYROID AND LATER WITH THYROXINE

Case no.	Sex	Age (yr.)	Thyroid		Cholesterol (mg. per 100 ml.)	P.B.I. (µg. per 100 ml.)	Thyroxine		Cholesterol (mg. per 100 ml.)	P.B.I. (µg. per 100 ml.)	Weight loss (lb.)
			Dose (gr.)	Years of treatment			Dose (mg.)	Weeks of treatment			
1	M	57	$1^1/_2$	4	400	1·7	0·15	8	290	4·4	29
2	F	71	2–3	8	260	0·7	0·2	10	200	7·0	11
3	F	65	2–4	8	552	2·3	0·2	8	299	4·5	9
4	M	67	1–3	5	360	2·4	0·2	6	230	6·0	12
5	F	70	3–4	9	600	1·7	0·2	4	340	6·6	4
6	F	62	1–3	10	299	1·6	0·1	8	164	3·9	3
7	F	59	4	8	420	2·0	0·2	3	215	7·0	5

tablets, we decided to document this increasingly frequent clinical syndrome.

The table gives the details of seven such cases:

All, when first seen, were obviously undertreated, and all were alleged to have been taking thyroid—usually thyroid *B.P.*—in the doses stated, and usually in increasing doses over the years. Sometimes it was possible to obtain the tablets which they were supposed to have been taking. All patients were transferred to an approximately equivalent dose of thyroxine (gr. 1 thyroid=0·1 mg. thyroxine), and further observations of clinical state, serum-cholesterol, and protein-bound iodine were made at various intervals. All these patients, and a number of other cases which were not fully documented, responded clinically and biochemically. A typical response is shown in fig. 1.

It could, of course, be said that these patients had swallowed their thyroxine tablets regularly but not their thyroid tablets. To test this, further observations were made on case 4:

This elderly patient had apparently taken thyroid *B.P.* for 5 years before he was first seen, his own doctor having ultimately increased the dose to gr. 3 daily. His weight was recorded a year before we saw him, and he had gained 29 lb. and become obviously hypothyroid, and his serum-cholesterol was 300 mg. per 100 ml. and protein-bound iodine 2·8 μg. per 100 ml. He was admitted to the ward, and, under observation, given his own thyroid tablets *B.P.* in a dose of gr. 3 daily for four weeks, after which he had put on 3 lb. in weight, his serum-cholesterol rose to 360 mg. per 100 ml., and his protein-bound iodine fell to 2·4 μg. per 100 ml.—all small but inconsequential changes. Treatment was then started with thyroxine 0·2 mg. daily (less than the ostensible equivalent dose, but, in the circumstances, a very large starting dose), and in 6 weeks he was clinically euthyroid and had lost 12 lb. in weight, his serum-cholesterol had fallen to 230 mg. per 100 ml., and his protein-bound iodine had risen to 6·0 μg. per 100 ml. (fig. 2).

DISCUSSION

There are a number of possible explanations for the apparent relapse of patients on thyroid *B.P.*, and for their subsequent response to thyroxine:

1. The thyroid tablets prescribed may not have been swallowed by the patients. This undoubtedly applies to some cases where the tablets appear to have been " inactive ", but it is not always the cause and it was specifically excluded in case 4 above.

2. The thyroid *B.P.* tablets supplied may not be biologically active, or the order of biological activity may not be that expected—e.g., the *B.P.* assay procedure is not a valid reflection of the biological activity of thyroid *B.P.*

3. The patients cannot absorb the hormone contained in the thyroid tablets.

4. The tablets used by the patients, possibly potent at the time of manufacture, have deteriorated, losing their biological activity.

I would submit that the principal factors which make it important to recommend thyroxine rather than thyroid *B.P.*, are related to (2), (3), and (4) above.

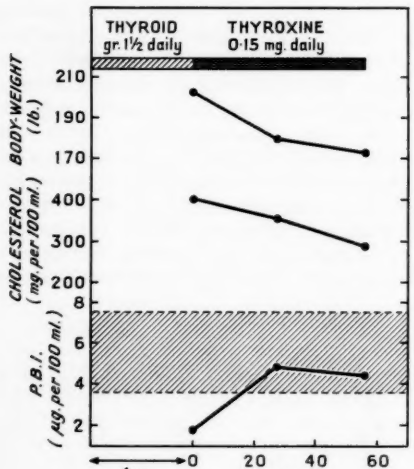

Fig. 1—Response of hypothyroid patient on transfer to thyroxine from thyroid *B.P.* tablets. (Case 1; male, aged 57.)

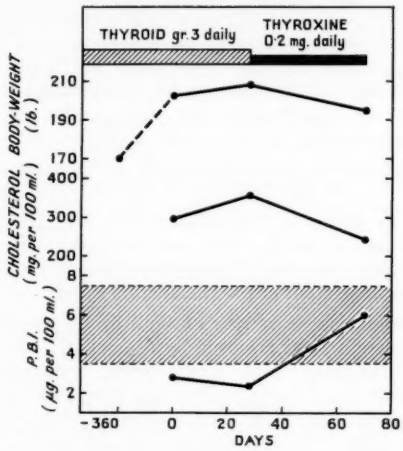

Fig. 2—Response in case 4 (male, aged 67) after continued treatment with thyroid *B.P.*, and subsequent transfer to thyroxine.

Validity of B.P. *Assay*

Periodic doubts have been expressed for years about the validity of the present methods of standardising thyroid extracts, both in this country and in the U.S.A. (Gaddum and Hetherington 1931, Means et al. 1933, Frieden et al. 1949.) Thyroid is assayed chemically both here and in the U.S.A. The *B.P.* assay specifies a content of 0·1% of iodine in combination as thyroxine, and the *U.S.P.* assay is even less specific, demanding 0·17–0·23% as iodine in thyroid combination.

By and large, as Gaddum (1953) has put it, " this gives a good enough index of activity ", but he and all other authorities state that " it is very important to use a standardised preparation ". Goodman and Gilman (1958) write: " The physician should make certain of the potency of the particular preparation which he employs, and consider this factor in arriving at the proper dosage. Particular care regarding dosage should be exercised if any change is made in the brand of thyroid employed. The entire problem can be circumvented by the use of official preparations ". This emphasises, by implication, the extent to which non-official preparations may, in fact, be distributed and used, and it also implies that standardisation by the official assay procedures guarantees an acceptable level of biological activity.

The chemical assay procedures used here and in the United States, being basically dependent upon thyroidal iodine content, are therefore only indirect indices of probable biological activity. But it has been shown

(Stasilli and Kroc 1956) that, regardless of the geographic origin or method of preparation of the extracts, beef preparations of thyroglobulin contained only about 50% of the biological activity of pork thyroglobulin on the basis of either total (*U.S.P.*) or " thyroxine " iodine (*B.P.*). Clearly if the beef preparations were diluted to meet *U.S.P.* or *B.P.* specifications for thyroid, they would still have only half the biological potency of pork preparations comparably diluted.

These observations have very great significance because they imply that, without a knowledge of the species source of the thyroid, the assay cannot reflect biological activity. In fact, Thompson et al. (1935) showed that, when comparing maintenance doses in the same hypothyroid patient, sheep and beef thyroid had less effect than hog thyroid in doses containing the same total amount of iodine.

Under the conditions of commercial marketing of thyroid tablets, there is no constancy in the species source from which the thyroid is derived and from which the tablets are made. Some American manufacturers use pork thyroid exclusively, while others use beef. British thyroid preparations are not necessarily derived from constant sources of supply, and for weeks or months a manufacturer might market tablets derived from pork thyroid, and thereafter tablets made from sheep or beef thyroid. The latter would, on the available evidence, have only half the biological activity, as measured by the goitre-prevention method in the rat, of the pork thyroid tablets. But both batches would equally conform to the standards of the *B.P.* assay for thyroxine iodine. The differences in potency of different thyroid extracts may well be due to variation in the proportions of triiodothyronine present in the preparations. Under such circumstances many patients' maintenance requirements may appear to alter.

It is probably significant that leading manufacturers of thyroid tablets in the United States use biological assays as well as iodine determinations in standardising each batch of their products, for " it has been demonstrated that iodine content alone may not reflect the biological activity of the product if different species of animals are used as a source of thyroid. By biological testing we insure uniform biological response to each tablet of our thyroglobulin " (Wermer 1958). It is not the custom of British manufacturers to submit all batches of thyroid tablets to a biological assay, and neither the *B.P.* nor *U.S.P.* requires or describes a biological assay.

Absorption of Hormone and Loss of Potency

The patients certainly have no inherent difficulty in absorbing active hormone, for an effective biological effect can be readily demonstrated with active thyroid tablets, or with thyroxine. But the possibility remains that, under normal or abnormal conditions of storage, the tablets may become so desiccated that they may not disintegrate and may not be absorbed. Some manufacturers market thyroid as an enteric coated preparation, and, like many similar preparations, they may occasionally pass through the gut intact and be found in the fæces. There is no evidence that this can happen with uncoated thyroid tablets.

Even if a tablet, because of its pharmaceutical composition, becomes non-absorbable, it may still have biological activity when crushed and assayed. When Jackson (1957) reported the difficulties associated with prescribing thyroid tablets in the United States, and advocated that, because some thyroid preparations are not reliable, none should be dispensed after three months' storage, he was immediately attacked by two manufacturers who showed that their products retained biological activity and potency when repeatedly tested over many years (Hubata et al. 1958, Wermer 1958).

In my own experience of the activity of thyroid tablets, no further supplies of the tablets which case 4 had taken were available for assay, nor could the batch number be determined. The manufacturer of the tablets used by two other patients (one not included here, and case 2) submitted sample tablets from the patients' supplies to biological assay, using the goitre-prevention technique in thiouracil-fed rats. The thyroxine activity of the first patient's tablets was of the order implied by the thyroxine-iodine level, as determined by *B.P.* assay. The assay on the tablets from case 2 showed activity of about 70%, but the statistical limits of the test were such that it might have been much higher or lower. (The fiducial limits, with $P=0{\cdot}95$, were 32·6–97·4 when the assay was based on moist thyroid weight, and 39·9–102·6 when based on dry thyroid weight.) The important point is that demonstrable *clinical* inactivity was not associated with constantly demonstrable biological inactivity when measured by the goitre-prevention technique in the rat. There is, of course, no knowing which biological assay procedure most closely resembles clinical biological activity in man. Calorigenic biological assays give comparable, though not necessarily the same, results as antigoitrogenic assays; but, in this instance, the vital biological assay is the biological response of the hypothyroid patient.

Accepting that, in Gaddum's phraseology, the *B.P.* assay gives a " good enough index of activity ", one can never be certain that the biological potency will remain unimpaired with time, because the substance is not a pure compound, and, under suboptimal conditions of storage, it may break down. The clinical impression of instability, as contrasted with non-absorption, of some thyroid preparations is difficult to document, and Owren's (1951) finding of preparations of dried thyroid with little or no clinical activity, even from many manufacturers, could have been due to ineffective absorption. As already mentioned, biological activity and potency may be retained for many years under some conditions (Hubata et al. 1958, Wermer 1958).

One must accept, however, that the conditions of storage in many pharmacies and most patients' homes, do not meet the stipulated recommendations. The *British National Formulary 1957*, for example, recommends that " they should be kept in containers which prevent access of moisture, in a cool place ", whereas many patients keep their tablets in extraordinary and bizarre receptacles, which are often damp. Pure thyroxine, particularly in tablet form and having the internal mass protected by the external layers and excipient, might be expected to be more stable, but it too should probably be kept dry and away from light. In several cases of apparent inactivity of thyroid tablets, the patient has obtained his supplies of tablets from small, isolated, or rural pharmacies where the turnover on the shelves is probably lower than in busy city pharmacies.

Whatever the cause of lack of clinical biological potency —be it non-absorption of hormone, or deterioration of the tablet with loss of biological activity, or even very deficient biological activity at the time of manufacture because of unreliable assay procedures—the fact remains that some

patients taking thyroid tablets do not gain the expected biological effect, and yet they respond adequately to alternative therapy. The vogue a few years ago in the United States for the diagnosis of " metabolic insufficiency ", which is now fortunately discredited (*Lancet* 1960), received impetus from a proportion of patients who were said to respond to triiodothyronine but not to thyroid extract. Some patients who did respond to treatment with triiodothyronine were undoubtedly truly hypothyroid, having for the first time effective replacement therapy when they were given triiodothyronine, their previous thyroid tablets having been ineffective. Thyroxine was not usually given to these patients.

Many leading American thyroid clinics stipulate very precisely which particular brand of thyroid their patients are to have, this being necessary because of the unreliability of a number of commercial products. It is not unknown for patients of the Mayo Clinic to return their prescriptions to Rochester so that they may be dispensed at the pharmacy adjacent to the clinic, ensuring that the recommended brand is provided.

Relative Costs

As already mentioned, the relative " expense " of thyroxine has been used as an argument against its use:

The present retail cost of a hundred 0·1 mg. thyroxine sodium tablets is 3*s*., and the retail cost of a hundred gr. 1 thyroid *B.P.* tablets is 1*s*. 9*d*., in a national chain of pharmacies. According to the current lists of costs of British National Formulary and proprietary preparations, the total cost to the Health Service, in Scotland, of a hundred 0·1 mg. thyroxine sodium tablets is 4*s*. 4*d*.; the total cost to the Health Service, in Scotland, of gr. 1 thyroid *B.P.* tablets is 2*s*. 4*d*. for forty-eight, and less than 3*s*. for a hundred tablets. Costs are slightly but insignificantly different in England, owing to variation in drug tariff charges, and different levels of dispensing fees. Hospital costs are appreciably lower, a thousand 0·1 mg. thyroxine tablets costing 15*s*., and a thousand gr. 1 thyroid *B.P.* tablets costing 3*s*. 4*d*.

Thus whether the products are bought within or without the Health Service, the difference to the individual or to the State is about 1*s*. 3*d*. for a hundred tablets. More than 0·2 mg. of thyroxine daily is rarely required, although higher equivalent doses of thyroid are common, chiefly because 0·1 mg. of thyroxine is, on average, more effective than gr. 1 of thyroid. Allowing two tablets daily, a hundred tablets are sufficient for a 7-week supply, and the increase in cost approaches 2*d*. per week.

CONCLUSION AND RECOMMENDATIONS

Not only is there excellent evidence, in the literature and in clinical practice, of variability of efficacy of thyroid preparations but there is also ample evidence in favour of more extensive use of a refined and pure therapeutic product. In the treatment of true hypothyroidism *l*-thyroxine sodium can do effectively all that has been achieved by thyroid *B.P.* in the past, but tablets of thyroid may vary in their biological potency, as contrasted with their activity according to the *B.P.* or *U.S.P.* assays, because of the different species from which the thyroid is derived.

Thyroid tablets may lose their biological effectiveness in hypothyroid patients while possibly retaining some activity when tested biologically by the goitre-prevention technique in rats.

It seems appropriate, therefore, to suggest that:

1. If it is necessary to retain thyroid preparations in the next edition of the *British Pharmacopœia*, a biological assay for thyroid tablets should be specified.

2. Batches of thyroid tablets should be dated, and given a " shelf-life " after which they should not be dispensed.

3. Both the above recommendations would become redundant if the profession as a whole used thyroxine instead. There is ample pharmacological, therapeutic, and economic justification for recommending that thyroxine be used for all thyroid replacement therapy, to the exclusion of preparations of dried thyroid, including thyroid *B.P.*

My thanks are due to Prof. E. J. Wayne and Sir Derrick Dunlop, who have taken much interest in the results of this study.

I am indebted to Mr. K. L. Smith, of the bioassay division, standards department, of Boots Pure Drug Co., Ltd., for the biological assays on the thyroid tablets.

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THYROID EXTRACT

THE potency of different batches of thyroid tablets has often been queried, and the standards used for assaying them vary in different countries. To discuss such problems a meeting was held during the Fourth International Goitre Conference in London last July. Prof. E. J. Wayne (Glasgow) took the chair and the following were present:

Dr. Brown Dobyns (Cleveland, Ohio), Dr. D. Evans (National Institute of Medical Research), Dr. B. Garratt (standards department, Boots, Nottingham), Dr. Raymond Greene (New End Hospital, London), Dr. R. L. Kroc (Warner-Lambert Research Institute, New Jersey), Prof. A. Macgregor (Aberdeen), Prof. N. F. Maclagan (Westminster Hospital), Prof. R. Michel (Clinique Pharmaceutique, Paris), Dr. R. Pitt-Rivers (National Institute of Medical Research), Dr. Rulon Rawson (Memorial Hospital, New York), Dr. K. L. Smith (standards department, Boots), Mr. Selwyn Taylor (London, conference secretary), and Dr. W. R. Trotter (University College Hospital).

The discussion opened with the statement that there was evidence that preparations of thyroid were not always biologically active and it had been suggested that they might be abandoned in favour of synthetically prepared thyroxine. Since, however, the British Pharmacopœia Commission felt that many would go on using thyroid extract, satisfactory standards for it were essential. Harington's original thyroxine was racemic and did not produce a good metabolic response in patients; so, although it was originally inserted in the *British Pharma-*

copœia (1932), it was later removed. Since the synthesis of laevothyroxine by Borrows et al.,[1] its potency had been confirmed and this preparation was now in the *B.P.* The problems were whether or not dried thyroid extract should be retained in usage; and, if so, how it should be assayed—whether by the method of the *U.S.P.* or by that of the *B.P.*

Seven patients were described who became hypothyroid while taking an apparently adequate dosage of thyroid tablets *B.P.* These patients were assessed by clinical and laboratory methods and then given thyroxine until they became euthyroid. Was this because the thyroid tablets had lost their potency? The tablets were assayed, using the goitre-prevention assay of the *U.S.P.*, and they had been assessed as 70% potent. Possibly the tablets had not been completely absorbed. Another important finding was that the tablets had been assayed, one lot against each other and against thyroxine, and there was a difference in potency of $2^1/_2$ to 1 among the tablets themselves. One member thought that, though the potency of 70% had been confirmed, it could not be considered significant. The tablets had been ground up and not used whole in the assays, thus avoiding problems due to hardness or surface change. It was, however, pointed out that thyroxine is known to be light-sensitive, and if stored for a long time must be kept in the dark. The next French Pharmacopœia would have thyroglobulin in it: it would not be tested biologically, but the content of arginine would be used as a cross-check.

It was reported that when the United States Food and Drug Commission assayed some extremely old rancid thyroid tablets taken from a pharmacy shelf they were found to be fully active. Some of those present maintained that thyroid kept its potency no matter how old; but others disagreed with this statement, and said that old tablets were sometimes not so efficient, though it was difficult to be certain that the patient took them. Thus it might be better if the drug was bought in small quantities from a supplier who had a rapid turnover. The active principle in the tablets was denatured thyroglobulin.

The next point raised was: How do different brands vary in their potency, and are they all assayed biologically as well as by the *B.P.* or *U.S.P.* standards which are based on the chemical content of iodine? It appeared that only one firm was known to carry out biological assay on all its thyroid preparations. Even when careful bioassays were done on batches of 60 rats, the error was often plus or minus 25%. It was pointed out that it was also important to apply a disintegration test to tablets. In one factory chemical assay for thyroxine was made on regular batches, but even so it was possible for the diluent to be at fault. It was found that lactose can inhibit activity as much as 40%. It had also to be remembered that many non-thyroxine substances—for example casein with iodine—could give a positive result with these assays.

When it came to discussing the source of material for making thyroid tablets, assays showed that desiccated beef thyroid was half as potent as pork thyroglobulin. Many manufacturers used 60-70% pork and the remainder beef. Certain brokerage firms provided very cheap tablets which were only 20% of the standard maintained by other drug houses and might rate at only 14% on the goitre-prevention test. In addition, seasonal changes could account for variations in the potency of the thyroid.

1. Borrows, E. T., Clayton, I. C., Hems, B. A. *J. chem. Soc.* 1949, suppl. 1, p. 199.

The CHAIRMAN summed up the long and interesting discussion. Clinicians, he said, agreed that some specimens of thyroid extract were not as active as others. Why was this?

a. Were they never active in the first place—i.e., were they made from unsuitable animal material, from the wrong species of animal, at the wrong time of year, or from animals grazing on mineral-deficient land?

b. Had they been kept too long or been destroyed by exposure to light?

c. Had they failed to be absorbed? This was unlikely except when tablets were enteric-coated.

Certainly, in preparing tablets, lactose should not be used as a diluent and calcium phosphate should replace it. Where possible the French method of checking the arginine content might be used with advantage. What biological test would be most effective for these tablets? If the calorigenic one was too expensive, then goitre prevention was probably the one to use. Finally, it would be convenient to have only *l*-thyroxine sodium for prescription, since it could be expected to be uniformly potent; but would it remain so when stored? If not, then the expiry date should be given on the label and the conditions for storage should also be stated.

SELWYN TAYLOR.

Public Health

REACTIONS TO INJECTIONS OF DIFFERENT VOLUMES

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AT the request of Dr. W. C. Cockburn, of the public health laboratory service, a study was made in children attending welfare clinics and day-nurseries of reactions to injections of pertussis vaccine containing 20,000 million organisms in 0·5 ml. volume and in 1·0 ml. volume. The children in the study were allocated to one of two groups according to the date of birth.

Children born on odd days of the year were given 0·5 ml., and children born on even days 1·0 ml. The injections were intramuscular. 33 children received 0·5 ml.; they were given 94 injections. 45 children received 1·0 ml.; they were given 125 injections.

Crying at Time of Injection

After each injection a note was made whether the child cried. If it did, the duration of crying was noted as "short" or "long" (see table). Twenty-four hours after the injection the child was seen and local and general reactions were recorded. All observations were made by me.

SPELLS OF CRYING AT TIME OF INJECTION

Crying	0·5 ml. group (%)	1·0 ml. group (%)
None	24	3
Short	67	32
Long	9	65

General and Local Reactions 24 Hours After Injection

General reactions were rare in both groups. After about 8% of injections with 0·5 ml. and 17% of injections with 1·0 ml. the mother volunteered that the child was "slightly upset". This was the only general reaction noted.

Local swelling was present after 46% of injections with 0·5 ml. and 48% of injections with 1·0 ml. Local redness was seen in 13% in each group.

Conclusion

The results of this study confirm that giving pertussis vaccine in 0·5 ml. volume upsets children at the time of injection less commonly than does 1·0 ml.—presumably because the smaller volume of fluid distends the tissues less. There was no evidence that the general and local reactions twenty-four hours after injection were fewer with the smaller volume.

Respiratory Infections

The influenza epidemic shows no signs of abating. In England and Wales nearly twice as many (699) died from this cause in the week ended Jan. 28 as in the previous week (358). In the corresponding period last year only 43 patients died of influenza. 80% of the deaths were reported from the Midland and North-Western regions and the West Riding; 90% of those who died were over 55.

Virus of variety A2 has been isolated.

The epidemic appears to be spreading to Wales [1]; east Glamorgan and Monmouthshire have been the worst affected areas.

Prevention of Tuberculosis

The Minister of Health [2] has informed local health authorities that he is prepared to approve extension of B.C.G. vaccination to children aged 10 and upwards.

Up till now vaccination has been offered to medical staff and nurses in hospitals, to close home contacts of tuberculosis cases (at the discretion of chest physicians), to students attending universities, teacher-training colleges, technical colleges, and other establishments of further education, and to schoolchildren of 13 and upwards. The Minister stresses the importance of ensuring that all tuberculin-negative children are vaccinated before leaving school.

1. *Guardian*, Feb. 4, 1961.
2. Circular 6/61.

Infectious Diseases in England and Wales

Disease	Week ended January			
	7	14	21	28*
Diphtheria	4	5	3	4
Dysentery	389	385	418	530
Encephalitis:				
Infective	2	3	3	3
Postinfectious	2	4	5	2
Food-poisoning	93	105	107	95
Measles, excluding rubella	15,989	13,591	12,618	14,743
Meningococcal infection	26	17	20	26
Ophthalmia neonatorum	13	18	26	14
Paratyphoid fever	4	4	2	1
Pneumonia, primary or influenzal	742	717	771	1121
Poliomyelitis:				
Paralytic	2	2	2	3
Non-paralytic	..	..	4	..
Puerperal pyrexia	157	190	160	194
Scarlet fever	416	362	422	476
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	301	416	412	357
Meninges and C.N.S.	5	1	6	2
Other	30	65	47	47
Typhoid fever	..	2	2	1
Whooping-cough	968	891	759	937

* Not including late returns.

In England Now

A Running Commentary by Peripatetic Correspondents

"It's them electric razors wot causes cancer of the lung." Mr. Todd emphasised the point with an extra jab of his shaving brush against the throat of the fellow in the chair. I was next, but only for a haircut, so I poked one ear round the edge of the morning paper and waited for Todd to develop today's theme: quite a change from his usual football pools.

"Yes," he went on, "Why do you think five or six men get lung cancer compared with every one woman wot does?" Some sort of reply about smoking bubbled out of the lather. Todd snorted. "Not on your life, Sir! Them womenfolk smoke just as much as us men these days, some of them a tidy sight more. No wonder the housekeeping money goes like it does. You don't tell me six times as many men smoke as women. No, it's them electric razors." He gave his old cut-throat a vicious strop, and turned back to the chap in the chair.

"Now see, Sir, it's like this. Suppose I was clipping your moustache with the scissors, and one of the sharp bits of hair jumps up in your eye. You know how it prickles. Well then, when you use an electric razor there are hundreds of little sharp bits of your whiskers wot get ground up, and you sucks some of them up your nostrils and in through your mouth. You can prove that by blowing your nose and see some of them come back. Just like a perishing vacuum-cleaner is your noseyfarincks, as our doctor calls it. And all them little sharp bits of hair get sucked down into your tubes, and stick in the lining of your lungs. Worse than sandblasting it is; proper chronic irritating, I say." Mr. Todd moved round towards the other cheek.

"But that's not all there is to it. Them whiskers, wot your electric razor grinds off sharp and dry, ain't clean whiskers. No, Sir, you've been pushing that face of yours all day through them diesel fumes out of our buses, and maybe streaming tobacco smoke across your cheeks as well. If you was to peer at them whiskers through a magnifying glass it'd look like a spider's web with the morning dew on it. Only it wouldn't be dew. It'd be dollops of that little old three four Ben's Pie whatnot; you know, the cancer stuff wot does no good to mice. So you sucks it all down into your lungs with the help of the Electricity Board. There's your reason for more and more lung cancer, with them pylons creeping all over the country."

The last strokes of the master hand were in full swing. "And, how many ladies use electric razors on their faces? There's your difference between men and women getting lung cancer." The towels were peeled off, and Mr. Todd straightened his back. "No, Sir, you stick to the old soap and water. Let me fix you up on weekdays, and I'll sell you some razor blades for Sunday. Thank you very much, Sir. Next please."

* * *

Alphabetical classification is usually simple enough; but where there is a competitive spirit at large, the struggle to be first may complicate things. Nowhere, I suppose, does vaulting ambition so o'erleap itself as in New York; and one evidence of this is to be found in the first few pages of the A's in the Manhattan telephone directory. It is not that system is lacking; on the contrary, the system is more profound and subtle than one had imagined possible. It is merely that profusion has tested old principles to the limit. Everyone wants to be A and in addition, to be *more* A than the next man.

The first entry of all, with stark dignity, is simply the letter A (with an address). After several A's we come to hyphenated-A, A-Art, and then, in turn, to double-A, triple-A, and quadruple-A. With a brief swerve aside, we pass through:

AAAA-AAAA ofc mechs
AAAAAA AA BB EE Moving & Storage Co.
AAA BBB ABC Typewrtr Co.

before getting back to the mainstream with sextuple-A. At this stage the healing arts make a modest bid with seven A's:

AAAAAAA Chiropractic & Massage Center

and the summit is finally reached, with nine A's by:

AAA AAA AAA Amer Flag Decratg Co.

From then on, the principle is evidently different, for the number of A's begins to dwindle. One perceives intuitively but dimly the subterranean workings of a master mind as one's eye travels down through a long list of ABC's only to embark on two pages of names beginning with A & or with A-1. At last, however, there appears the name of the first human survivor of this alphabetic barrage—Albert Aach. I think great credit is due to Mr. Aach, for he has sailed the perilous seas of private enterprise and safely come to port; but nevertheless, perhaps our tribute should rightly go to the anonymous Napoleon whose mind, shuffling and sorting the varied strands of greed, aggressiveness, and self-display, has contrived to preserve so much order and justice in what is, after all, one of the most-read books in the world.

* * *

A consultant came across a small boy struggling with the chain of his bicycle, which had become disengaged from its sprockets. Good-naturedly he lent a hand, replaced the chain, and tightened it expertly by adjusting the back hub. "There," he said, "that should be all right now. Of course I cannot absolutely promise that it will never happen again. Suppose you let me see it in a month's time?" At the end of the month he exclaimed, "Capital, capital," beaming and striking the saddle three times with his pencil, "no trouble? Capital. Let's see it again in another month's time." And so it went on, but the small boy, fearful that his bicycle might fail him when far from home, lost all zest for cycling, and soon gave it up altogether. But he continued to take his machine to the consultant each month for quite a long time.

* * *

A great man came to lecture to our students. This has led to a new word in their vocabulary—a heneagedote.

* * *

I used to be in the happy position of not knowing my bank manager. Not only did I not always know what he looked like, but I often did not even know the name of the current one. My colleague with a four-figure overdraft used to call in to see his manager every three months or so to pass the time of day, to discuss almost on Christian name terms the weather, politics, the education of their children, and so on, slipping in somewhere just by chance a word about the continuation of the overdraft facilities. I used to envy their familiarity. And then our hot-water system blew up. We had the choice of patching it up on the cheap, or doing the job properly. Having found out the name of my bank manager, I verified his identity, and made an appointment to see him. He greeted me like an old friend across the desk on which was displayed my history—all in black figures on a large sheet: he must have thought greedily of all those red figures which might soon be spreading down towards the foot of the page. He expressed the hope that I would get my plumbing put right, with his assistance. The rot set in there and then. Two years later it is comforting that it only needs a three-figure overdraft for my passage through the doorway to be greeted by a smile; and as I pass along the counter to find a vacant desk, each cashier in turn looks up from his pile of notes, and without interrupting his counting gives me an affable "Good morning, Sir". They are all of them pleasant and civil gentlemen, but maybe it is only natural that their pleasure should be heightened by the patent reassurance that I am in good health, and that the interest on my overdraft will continue to come in regularly.

* * *

re Medical Physiology and Biophysics. Edited: Ruch and Fulton. 1960.

Certainly the spelling
doesn't help one very much
When setting out to buy the book
of Theodore C. Ruch.
But the asking would be easier
if you only knew
That by all his colleagues
he is called Ted Ruch.

Letters to the Editor

REPRINTS

SIR,—Through you we wish to seek guidance in procedure.

Formerly when a paper was published the author estimated the number of reprints he would require, depending upon the importance of the subject, and the likelihood of interest being aroused among workers and colleagues unable to obtain the journal concerned; and he would order a suitable number. A few requests came from abroad, but only from those working on the same subject.

Now, however, things have changed. Recently we published a paper. We have been inundated with requests on printed cards for reprints, demanding 1, sometimes 2, and occasionally 3 copies, from individuals, frequently non-medical, with illegible signatures, often from unknown institutions. The bulk came from the U.S.A. With a personal letter from someone working in the same field, the answer is easy; but when the request comes on a stereotyped card, sometimes unsigned, asking for "a reprint of your article published in such and such a journal" . . . "and other relevant papers published by you"—without even mentioning the title, what does one do?

I should value guidance; our experience cannot be unique.

Cumberland Pathological Laboratory,
Cumberland Infirmary,
Carlisle. J. STEVEN FAULDS.

SHORTAGE OF RADIOGRAPHERS

SIR,—I am convinced that the present shortage of radiographers, like all other shortages in the medical ancillary services, is due almost entirely to lack of suitable publicity. In this school we try to have an annual careers evening when we invite specialist speakers to the school to talk to the girls and to their parents about the opportunities available in the various professions.

On one such evening a radiographer was sent to us by Dr. Osborne [1] as part of his experimental recruiting drive. I would stress the value of having a *specialist* lecturer. A general talk on careers, no matter how well delivered, can never have the same appeal to young people as direct contact with a vital—and preferably young—happy person who is herself actively engaged in the particular profession. Detailed questions can be asked, and up-to-date information given by a lecturer the girls can feel is not too far removed from modern working conditions in the world as they see it.

The radiographer's lecture aroused very real enthusiasm; and 2 groups of girls were invited to visit a department of radiography where further questions were answered. All considered that they had obtained a realistic view of the training and work. Several of our girls are already training at Guy's, The Royal Free, and Middlesex Hospitals; and others are still at school awaiting admission, having been accepted for training. All are very happy and content; and were it not for the personal contact made possible by the courtesy and interest of Dr. Osborne I know they would not have considered radiography seriously. It would have been yet another of the "vaguely possible" careers, long since forgotten. Films and slides are very useful; but above all, it is personal contact with the right sort of lecturer that attracts the worthwhile recruit.

In the same way I am indebted to the Royal College of Surgeons who admit sixth- and sometimes fifth-form pupils interested in medicine to their excellent lectures in the Christmas holidays. The girls from this school now training for medicine have told me that they were greatly helped by these lectures, and were keenly aware of the real and kindly interest of the lecturers and the staff. Other girls who were not intelligent enough for a full medical career asked me to suggest other openings in associated professions. This has led to quite able pupils undertaking medical laboratory work, orthoptics (1 girl—but this service is poorly publicised), occupational

1. *Lancet*, 1960, ii, 96.

therapy, and physiotherapy. These talks are most successful if begun during the fifth-form year. It is too late to leave it till the sixth form as quite often able girls with the right personal qualities will have drifted off into easier and less worthwhile employment.

Orange Hill Girls' Grammar School, Edgware, Middlesex. J. ENID WOOD Headmistress.

PEMPIDINE

SIR,—I am puzzled that Dr. Kitchin and his colleagues [1] conclude from their therapeutic trial of pempidine on 18 hypertensive patients that they "cannot recommend it for controlled trials". Controlled trials to establish what? Their own results show that the drug often controls blood-pressure, although it causes various unpleasant symptoms. Do they mean a controlled trial to establish whether long-continued treatment with pempidine influences the prognosis of patients with high blood-pressure? McMichael and his coworkers [2] have shown that the prognosis of malignant hypertension is greatly improved by treatment; and recently Smirk [3] and his colleagues reported an improved prognosis for malignant hypertension, patients with grade 3 retinopathy, and possibly for some less severe cases as well. Both McMichael and Smirk used pempidine and mecamylamine in their hypertension clinics.

I think it is reasonable to regard pempidine and mecamylamine as established and useful therapeutic agents. They have the well-known disadvantages inherent in drugs which block the parasympathetic system, but these troubles can be partly overcome by use of parasympatheticomimetic drugs. After the initial difficulties of accommodating to the regime most patients seem to tolerate it well. At Hammersmith Hospital results with pempidine and mecamylamine have been distinctly better than those reported by the Glasgow group [1 4]; and we still have 71 patients being treated with them. I have analysed the records of these patients:

Indication for pressure-reduction	*Control of blood-pressure*			
	Pempidine		*Mecamylamine*	
	Satisfactory	*Fair*	*Satisfactory*	*Fair*
Malignant hypertension ..	8	4	3	2
Grade-3 retinopathy ..	14	4	5	2
Hypertensive heart-failure ..	2	0	2	0
Other severe hypertension ..	10	3	6	6
Total	34	11	16	10

All of them before treatment had a blood-pressure of at least 220/120 mm. Hg; and often it was much higher. If we regard a reduction of the standing blood-pressure to 160/100 or less as "satisfactory control", and at least a 20 mm. fall in diastolic pressure as "fair control", 76% of the patients on pempidine and 62% of those on mecamylamine were satisfactorily controlled. All the remaining patients had fair control. The average duration of treatment was 2 years and 1 month for the patients treated with pempidine, and 3 years and 10 months for those treated with mecamylamine. These patients had severe disease, 46 of 71 having had papillœdema, exudative retinopathy, or left heart-failure, and doubtless if untreated many would not be alive today.

Two qualifications must be made. Firstly, some patients who had suffered severe symptoms from parasympathetic blockade are now being treated with guanethidine and do not load the figures, although by no means all who were transferred to other drugs had had poor control of their blood-pressure. Secondly, many of these patients might have been managed with the earlier drugs—for example, hexamethonium or pentolinium. But the amine ganglion-blocking drugs have the advantage over quaternary ammonium compounds that they are fully absorbed when given by mouth, and drug resistance is uncommon. Pempidine eliminates the very real difficulties encountered with some patients who had irregular control of their blood-pressure because of fluctuations in the absorption of pentolinium, or who had required mounting doses of the drug to maintain effective control.

The differences between pempidine and mecamylamine are small; but the more rapid excretion of pempidine is an advantage for patients with poor renal function, or those with threatened paralytic ileus. If you get into trouble with pempidine you can usually resolve it faster. The plasma-concentrations of pempidine after a given oral dose are reproducible[5]; and clinical experience has demonstrated that the amine ganglion blockers have the most consistent hypotensive effect of any of the potent pressure-lowering drugs. It is true that these various factors are individually of only moderate importance, but together they are of considerable significance in the long-term clinical management of patients. The experience of Somers, who treated 37 patients with pempidine, has been similar to our own.[6]

Until the ganglion-blocking drugs are entirely ousted (and guanethidine, although very useful and promising, has not yet quite done that) they will have a place in the treatment of some severely hypertensive patients. Despite the rather gloomy report of Dr. Turner and his colleagues, I would advise pempidine or mecamylamine as the first alternative to guanethidine in the treatment of hypertensive disease which directly threatens life. For some patients with occlusive vascular disease on guanethidine the fluctuations of pressure-control on exercise may be dangerous, and for them the ganglion-blocking drugs may be the first choice.

Postgraduate Medical School, London, W.12. C. T. DOLLERY.

RESPONSIBILITY IN HOSPITALS

SIR,—In your issue of Jan. 28 you report Mr. T. G. Lowden, of Sunderland, as contributing to the symposium on responsibility in hospitals a story of Cinderella with a cut eyebrow, lightly tossed from hospital to hospital as a technical misfit, until at last in the plastic unit, miles away from its parent children's hospital, the necessary repair is neatly executed. Of course it is meant to be a sad story but to me it is sadder, much, than seems to have been intended, for the reason that neither its author nor anyone in it appears even to think of that other Cinderella, little Cinderella's own doctor. "Oh, Sind," said an Ugly Sister to the inquiring Prince, in a transatlantic version of the story, "she's away in the grill-shack, fixing bacon and beans."

Have we really reached the point at which all concerned assume that the family doctor cannot repair a cut eyebrow, though he will probably be asked next day to certify that the child is unfit to attend school?

Crockham Hill, Kent. LINDSEY W. BATTEN.

SIR,—Dr. Tait, in his letter last week, makes a very far-seeing proposal for reducing cost and inefficiency in the National Health Service, when he suggests reducing the general practitioner's list to 1000, quadrupling the capitation fee, and giving him a measure of responsibility in the hospital care of his patients.

Can he conceive of a politician with the breadth of vision to see, let alone persuade the Treasury, that by spending four times as much on the general-practitioner service he could save a far greater sum in hospital costs?

Such a step would involve fundamental replanning of the whole balance of the N.H.S. and would convert it into a true health service, from the ill-health service it now is.

1. Kitchin, A., Lowther, C. P., Turner, R. W. D. (1961) *Lancet*, Jan. 21, 1961, p. 143.
2. Harington, M., Kincaid-Smith, P., McMichael, J. *Brit. med. J.* 1959, ii, 969.
3. Hodge, J. V., McQueen, E. G., Smirk, H. (1961) *ibid.* Jan. 7, 1961. p. 1.
4. Kitchin, A., Lowther, C. P., Turner, R. W. D. *Lancet*, 1957, ii, 605.
5. Dollery, C. T., Emslie-Smith, D., Muggleton, D. F. *Brit. med. J.* 1960, i, 521.
6. Somers, K. *ibid.* Jan, 7, 1961, p. 13.

Should that step be taken, I would be the first to apply to rejoin a scheme from which I was forced to resign two years ago by sheer pressure of work; but, unless it is taken, I shall continue in general practice outside the N.H.S.

Kingston-upon-Thames. CHARLES STEER.

BRONCHITIS AND THE MINISTRY OF LABOUR

SIR,—Your annotation (Jan. 21) contains important information and suggestions. The provision of sheltered workshops for those disabled by bronchitis is a tempting objective for anyone facing the problem of finding employment for breathless patients.

The one objection to this scheme is the inevitably high mortality of the inmates, which might become so well-known that new entrants would assume prematurely that their fate was sealed. For this reason it seems better to find jobs for disabled people in the general industrial community.

Although this may be difficult, it is by no means impossible and well worth greater efforts.

Nottingham. W. K. S. MOORE.

SALT AND WATER RETENTION IN HEART-FAILURE

SIR,—In your leading article of Jan. 28 you state that aldosterone antagonists "have remarkably little diuretic action in heart-failure". Without qualification this statement is misleading.

The antagonists may have little diuretic action in *uncomplicated* heart-failure. In patients with advanced cardiac œdema, resistant to other diuretics, they have often produced a useful diuresis when supplementing the previously ineffective measures. Inevitably in some patients the cardiac output and glomerular filtration are so reduced that no therapy is likely to be effective. For this reason, the addition of spironolactone to an ineffective diuretic regime is less consistently effective in cardiac than in cirrhotic œdema; but many cardiac patients previously resistant to thiazides and mercurials have responded to the addition of spironolactone, and some of these have become œdema-free after a massive diuresis. When we made spironolactone available in May, 1960, we published an account [1] based on 7 separate investigations; and similar successful results have since been reported in several published and many unpublished reports. Jose [2] treated 50 patients with advanced cardiac œdema and reported a "significant and practical improvement in results" in two-thirds. There are other reports [3–10] of major diuretic effects in resistant cardiac œdema. Spironolactone acts slowly; therefore it is important to use it for a long enough time. You refer to a report [11] in which the duration of treatment was too short, at a time when supplies of the drug were inadequate.

We emphasise,[1] as you do now, that excessive sodium reabsorption in the proximal tubule appears to be the main factor in the development of cardiac œdema, and that this should be treated with drugs such as mercurials and thiazides which act upon the proximal tubule. You point out that "aldosterone secretion is sometimes increased" in right-sided heart-failure and that this can be expected to "make the condition worse". This appears to be one important factor in the development of resistance to diuretics, and it can now be overcome. There is another factor which can now be corrected. Some patients with resistant œdema have a defect of water metabolism. Before the aldosterone antagonists were available, corticosteroids were sometimes given to correct this, but the results were often disappointing. Now diuresis has been achieved in such patients by the use of the triple combination of thiazide, corticosteroid, and aldosterone antagonist, even though combinations of any two of these measures may have failed.[12] This is consistent with the hypothesis that both aldosterone and defective water metabolism may be factors in the development of resistance to diuretics.

Friedberg, in a recent authoritative review of the treatment of heart-failure and the use of diuretics,[13] commented that (when spironolactone is used) "resistance does not appear to develop despite continuous usage" and "its greatest value has been found in refractory cases in which it has been employed with thiazide drugs and prednisone".

G. D. Searle & Co. Ltd., High Wycombe, Bucks. G. R. VENNING Medical Director.

DEATHS UNDER DENTAL ANÆSTHESIA

SIR,—My experience of halothane ('Fluothane') is confined to general dental practice and does not cover such a large series as a hospital dental consultant might see.

Halothane provides better anæsthesia, better operating conditions, and complete recovery more rapidly than nitrous oxide and oxygen.

The cost (borne in dental practice by the practitioner) varies between 1*s.* 6*d.* and 2*s.* per case. My Goldman halothane vaporiser has proved unsuitable for storing fluothane between cases—I lost 20 ml. in one weekend, due to evaporation.

What the literature does not make clear is that cases resistant to halothane are encountered. 2 patients of mine, both heavy drinkers, responded vigorously to the stimulus of tooth removal; in responding they started mouth-breathing, which in turn lightened the anæsthetic further and thus increased their resistance. Operating on struggling patients is hazardous: teeth are likely to fracture and respiration become obstructed. Resistance apart, I am curious to know whether other dental anæsthetists think that mouth-breathing is more likely with halothane than with other anæsthetics.

Having seen these cases I now incline to the view that the resistant patient has his life unnecessarily imperilled by our persisting in the attempt to anæsthetise and operate. In this antibiotic age the dental anæsthetic is never urgent in the sense that operation is lifesaving. The resistant patient is best referred to hospital where techniques more elaborate than straight inhalation are available.

Even with the Goldman vaporiser halothane overdose is possible; and I have found short periods of apnœa common. My practice if apnœa persists is immediately to stop the halothane and nitrous oxide and to administer pure oxygen for about 15 seconds. So far this has never failed to restore respiration.

Finally, anæsthetists who are not familiar with the technique of administering halothane would be well advised to make sure that the dial-reading of the anæsthetic machine corresponds to the actual volume delivered. Regular service costs little and avoids the inaccurate dial-readings frequently found in anæsthetic equipment in dental surgeries.

Salisbury, Wiltshire. H. V. CAPSTICK.

SIR,—I agree entirely with the opinions expressed by Dr. Dinsdale (Jan. 28); but evidently he is not aware of the activities of the Society of Dental Anæsthetists.

At present comprehensive postgraduate courses in intravenous anæsthesia for dental surgeons are conducted, under

1. Aldactone. High Wycombe, 1960. (Searle Reference Manual no. 52.)
2. Jose, A. D. Cardiac Society of Australia and New Zealand, Nov. 29, 1960.
3. Laragh, J. H. *Postgrad. Med.* 1959, **25**, 528.
4. Vesin, P., Blanpin, O., Julien, C., Giboudeau, J., Renault, H., Cattan, R. Société médicale des hôpitaux de Paris, Oct. 23, 1959.
5. Vesin, P., Blanpin, O., Julien, C., Giboudeau, J., Renault, H., Cattan, R. *Bull. Soc. méd. Hôp. Paris*, 1959, **75**, 826.
6. Farrelly, R. O., Howie, R. N., North, J. D. K. *Brit. med. J.* 1960, ii, 339.
7. Tublin, I. N., Berman, L. B. *J. Amer. med. Ass.* 1960, **174**, 869.
8. Slater, J. D. H., Moxham, A., Hurter, R., Nabarro, J. D. N. *Lancet*, 1959, ii, 931.
9. Hoobler, S. W. *in* The Clinical Use of Aldosterone Antagonists (edited by F. C. Bartter); p. 155. Springfield, Illinois, 1960.
10. Morrison, R. S. *ibid.* p. 168.
11. Edmonds, C. J. *Lancet*, 1960, i, 509.
12. *Searle Research in the Service of Medicine*, 1960, **52**, 19.
13. Friedberg, C. K. *J. Amer. med. Ass.* 1960, **174**, 2129.

the auspices of the Society, by an acknowledged medical authority on the theory and practice of this very important branch of anæsthesia.

Full details of the activities of the Society are published in the dental journals.

A. G. LUNT
Hon. Secretary,
Romford, Essex. Society of Dental Anæsthetists.

THE OXFORD CLINICAL SCHOOL

SIR,—The letter from "Oxoniensis" (Jan. 28) does not greatly help. He says that much of the factual information contained in my letter is now happily out of date. Considering that in my account of the reasons why one promising student was lost to this school I only made two points, the use of the word "much" seems a little odd. Either one of the snags has been put right or both, not "much of them"! Perhaps "Oxoniensis" would be good enough to state which.

He says also that I have blurred the distinction between the University and the clinical school. It is true that one reason was the refusal of the University to exempt from first M.B. on G.C.E. at advanced level, and this in itself does not necessarily restrict the recruits to the clinical school. But in the case I mentioned it most certainly did. Surely if students are discouraged from going to Oxford University for preclinical studies they are less likely to proceed to the Oxford clinical school afterwards.

I should be glad if your correspondent could explain what has happened to alter the case. Perhaps at the same time he might come out from behind the smoke-screen of verbiage and tell us exactly what he meant by his last sentence: "Your own annotation [1] might be faulted on other grounds".

If he seriously believes this why does he not detail the grounds of complaint? Could it be that he is piqued by your remarks on non-cooperation between departments? I do not know Oxford well, but his letter has not made me any more keen to recommend it as a school for medical students.

CANTAB. SEMPER ANON.

A MASSIVE OVARIAN CYST

SIR,—I was interested to read Mr. Foreman's case-history (Nov. 26) of a massive ovarian cyst weighing 147 lb., and of Mr. Rose's example (Dec. 10) weighing 72 lb. I was asked to see a similar case when working with the Friends Service Unit in South Korea in April, 1955.

A South Korean woman, aged 47 (48 Korean age), was admitted to the gynæcological department of the Kunsan Provincial Hospital under Dr. Kim Ki Tae. Since the age of 25 (26 Korean age) she had noticed a gradual swelling of her abdomen, and suffered from increasing breathlessness on exertion. For the past two years the swelling had greatly increased in size, the patient was unable to leave the room in which she was living, and had become breathless on the slightest exertion.

In April, 1955, Dr. Herbert Bowles, gynæcologist to the Straub Clinic in Honolulu and adviser in obstetrics to the State Government of Hawaii, gave up his annual leave, flew to Korea, and without recompense assisted our Quaker medical team for a period of four weeks. His arrival was reported in the local newspapers and this was seen by the patient's relatives. Against the advice of the local herb doctors, who insisted that the patient would die if the tumour was removed, the relatives, who were all poor country folk, brought the patient in a wheelbarrow from her home in the Cholla Namdo Mountains some 60 miles away. The journey took $2^1/_2$ days.

She was a small wizened lady, about 5 ft. tall, who looked much older than 47. There was a large tumour filling the pelvis and abdomen, causing the ribs to splay outwards. Her respiration-rate at rest was 24 per minute, and the slightest exertion produced severe dyspnœa.

On April 8, 1955 (4288 Korean date), a massive cyst of the right ovary was removed by Dr. Kim Ki Tae and Dr. Herbert Bowles, and the general anæsthetic was given by myself. The operation lasted $2^1/_4$ hours, for there were dense adhesions between the abdominal wall, the small intestine, and the wall of the cyst. Giving the anæsthetic was a nightmare in my inexperienced hands, because the smallest dose of ether rapidly produced a deep anæsthesia. A trainee newspaper reporter (now with the *Baltimore Sun*) was in the building at the time, and I persuaded him to take a photograph of the operation (see figure).

The tumour measured approximately $36 \times 34 \times 14$ cm., and weighed 42·6 kg. (94 lb.). On sectioning, the massive tumour was seen to be a multilocular pseudomucinous cyst-adenoma. I could find no evidence of malignancy.

The patient made a good recovery, and was discharged from hospital 3 weeks after the operation. Her return journey was by bus, and the fare was paid by the American Friends Service Committee.

I am grateful to Mr. Donald Bremner for the photograph.

Westminster School of Medicine,
Research Laboratories,
London, S.W.1. JOHN S. CORNES.

DIASTOLIC BLOOD-PRESSURE

SIR,—The recording of blood-pressure findings appears to me to have reached a stage when an authoritative pronouncement should be made by the teachers and senior practitioners of medicine, surgery, and obstetrics.

As a country general practitioner who qualified in 1925, I have always been accustomed to recording the blood-pressure in the form 140/80 or 140 systolic 80 diastolic, the systolic being taken at the commencement of sound, and the diastolic at the time of change in its intensity.

A few years ago I noticed that some assurance companies were asking that the diastolic reading should be that at which the sound disappeared. On making inquiries of neighbouring physicians as to the generally accepted standards, I found that some were using the change of sound, some the disappearance of sound, and that in addition a third method was used.

I have been taught over the years that though the systolic value is so variable as to be of minor importance, the diastolic value is the bedrock of blood-pressure recordings. We are now in a position where at least three methods of recording the diastolic reading exist, and the readings must of necessity differ.

Especially when the importance of serial blood-pressure readings by different people is considered, this is a preposterous state of affairs. As an example I might mention the use of hypotensive drugs and the recordings of blood-pressure in toxæmia of pregnancy.

I suggest that an authoritative ruling be given to clarify the position; and that in the meantime—and that right urgently—some rules should be drawn up so as to indicate the mediums of diastolic values that are recorded.

I put forward as a tentative suggestion that the blood-pressure be recorded as 140/80/– or 130/–/70, the first meaning that the diastolic value is that taken when the

1. *Lancet*, 1960, ii, 1336.

1. See *Lancet*, 1960, ii, 968.

sound changes, and the second when the sound disappears. When the reading is given as 135/70 inquiries should be made as to the meaning of the figures given.

Petworth, Sussex. W. ANTONY BALL.

ORAL PROGESTOGENS

SIR,—In the past two years a number of new synthetic oral progestational compounds have appeared on the British market.

In addition to allylestrenol ('Gestanin', Organon), the compound reported by Dr. Field-Richards and Mr. Snaith (Jan. 21), there are now available norethisterone ('Primolut N', Schering, A. G.), norethynodrel ('Enavid', Searle), 17α-hydroxyprogesterone caproate ('Primolut Depot', Schering, A. G.), and dimethisterone ('Secrosteron', British Drug Houses). We are also conducting clinical trials on 4 other compounds from three companies, B.D.H., Imperial Chemical Industries, and Searle. In America and on the Continent there are many others available. We have had the opportunity of testing some of these on a few patients—e.g., 6α-methyl-17α-hydroxyprogesterone acetate ('Farlutal', Farmitalia).

Some of these progestogens are substitutes of 17α-hydroxyprogesterone. Others are related to testosterone or to *nor*-testosterone (not to 19-norandrostenolone as stated by Field-Richards and Snaith). It is likely that these 3 classes of compounds will have somewhat different effects. It is therefore of clinical interest to compare representatives of each group. The article by Field-Richards and Snaith gives the favourable impressions of experienced clinicians on one product. Unfortunately data such as measurements of menstrual loss, hormone assay, temperature charts, or histological reports on serial biopsies on which comparisons might be based, were not given.

Field-Richards and Snaith treated 5 cases of recurrent abortion with allylestrenol, and only 1 of these aborted. Naturally this number is not large enough to support any serious claim; but their favourable impression will no doubt be quoted by the manufacturing company in future advertising material. We have done serial assays of pregnanediol excretion in 54 women with a history of previous abortion. Only 8 of these aborted during the pregnancy studied. They had received only routine obstetrical treatment, being confined to bed at the time of their expected period. In particular no hormone preparations were given to any patient. In our opinion the value of any progestational compound in the treatment of abortion can only be judged by statistical analysis of a properly conducted double-blind trial with dummy tablets. Fortunately such trials are being done both in this country and in the United States, and scientific evidence may soon be available.

Field-Richards and Snaith treated 18 cases of menstrual disturbance with allylestrenol, and on the whole their clinical impression was favourable, although there were a few notable failures. We have treated 54 such cases with a variety of progestational compounds. 28 patients received a total of 80 courses of norethynodrel (enavid). 19 patients received a total of 54 courses of norethisterone (primolut N), and 7 patients received 16 courses of progestogens not yet commercially available. Each course consisted of 10–20 mg. of steroid daily from the 5th to the 20th day of the cycle. Each patient was curetted before starting treatment; and wherever possible this was followed by serial endometrial biopsy on the first day of menstruation, basal-temperature recordings, assay of the urinary excretion of pregnanediol and of œstriol, and estimation of total hæmoglobin loss in the menstrual flow. In this series we had eventually to do 5 hysterectomies; but in general we concur with Field-Richards and Snaith's favourable impression. The good results did not appear to be peculiar to any one compound. Some features not mentioned by Field-Richards and Snaith were evident in our series and may have occurred in their patients. These progestogens, like progesterone itself, are all pyrogenic. The basal temperature rises 0·4–1·0°F when treatment is started and remains elevated while they are taking the compound. When given in the proliferative phase all these compounds completely suppressed ovulation; no luteal rise of pregnanediol occurred. No patient became pregnant. The secretory change which occurs in the endometrium is due to the drug itself and not to progesterone from a corpus luteum. Nor can a histological picture exactly like a late secretory endometrium in the normal cycle be produced. The stroma and the endometrial glands are out of phase, the glands appearing less advanced than the stroma and not progressing to the highly serrated appearance of the normal premenstrual phase. Depending on dosage and drug a marked stromal reaction with cells almost decidual in appearance can be produced. The bizarre histological appearance sometimes produced by synthetic progestogens is well documented and has been described by German authors as "*starre Sekretion*".

Field-Richards and Snaith used allylestrenol in the luteal phase to enhance the secretory conversion of the endometrium. This is a promising approach but it remains to be shown what the effect of this compound is on the endogenous production of progesterone. Clearly synthetic gestogens do not mimic exactly all the actions of progesterone, and it may be that a pleasing histological picture is bought at the cost of physiological efficiency.

Finally, the term "allylestrenol" conveys very little other than an American flavour and it would be helpful if the company were to designate its product more fully.

Field-Richards and Snaith question the use of *nor*-testosterone compounds in pregnancy. Yet the very compound which they used is correctly described as 17-allyl-3-desoxy-19-*nor*testosterone.

Obstetric Medicine Research Unit, and Department of Obstetrics and Gynæcology, University of Aberdeen. ARNOLD KLOPPER MALCOLM MACNAUGHTON.

ESSENTIAL-FATTY-ACID CONTENT OF HENS' EGGS

SIR,—Dr. Gresham and Dr. Howard (Feb. 4) make a curious error when they imply that the diets of all free-ranging hens are identical. They are wrong to doubt the existence of regional differences. A hen ranging on bare, hard earth is likely to have a very different diet from that of a hen scratching on a compost-heap to which spent hops from a brewery have been added.

They are also wrong in supposing that the excellent analyses of Böttcher et al.[1] necessarily support their view that linoleic acid is atherogenic. If there is altered metabolism of the cells of the intima through a relative deficiency of essential fatty acid (E.F.A.), so that cholesteryl esters become actively transported into the wall, one might expect the more transportable cholesteryl linoleate to accumulate rather than, for instance, cholesteryl stearate. Böttcher has shown that the more extensive the atheroma the *less* the proportion of E.F.A. in the phospholipids of the intima. Schrade et al.[2] have shown that E.F.A. is decreased in the lipids of hyperlipæmic serum of those with atherosclerosis. The highest medical and scientific body of the American Heart Association released on Dec. 10 last a statement in which it concluded that "the reduction or control of fat consumption under medical supervision, with reasonable substitution of polyunsaturated for staurated fats, is recommended as a possible means of preventing atherosclerosis and decreasing the risk of heart attacks and strokes".

I continue on existing evidence to prefer to eat the type of egg that does not cause lipid to accumulate macroscopically on the wall of the aorta of chicks hatched from it.

Oxford. HUGH SINCLAIR.

1. Böttcher, C. J. F., Woodford, F. P., ter Haar Romeny-Wachter, C. C., Boelsma-Van Houte, E., Van Gent, C. M. *Lancet*, 1960, i, 1378.
2. Schrade, W., Boehle, E., Biegler, R. *ibid.* 1960, ii, 1409.

EXPERIMENTAL STAPHYLOCOCCAL INFECTIONS IN MAN

SIR,—In their article Dr. Foster and Dr. Hutt [1] state that they were unable to demonstrate any essential difference between the types of skin lesion produced by 5 different types of *Staphylococcus aureus*. The following experience may therefore be of interest.

In an investigation of tropical bullous impetigo in Singapore and Malaya [2] I carried out some experiments on the infectivity for skin of a *Staph. aureus* isolated from a bullous lesion as compared with another obtained from a boil on a patient in England. It had previously been observed that the behaviour of staphylococci from bullous impetigo differed in certain respects, from those isolated from other skin lesions in the Far East. For example, only 36% of impetigo staphylococci could be phage-typed, compared with 56% of those from other lesions. The latter organisms corresponded fairly closely with those carried in the anterior nares, of which 66% were typable. Also, epidemiological studies suggested that the spread of bullous impetigo was by direct contact, and that nasal carriage of staphylococci was of minor importance. Another difference between the two types of staphylococci lay in their sensitivity to penicillin. All of the impetigo strains (33 tested) were sensitive, compared with 73% (15 strains tested) of those from other lesions. The findings for staphylococci carried in the nose were identical with those for staphylococci from "other lesions". In general, while the staphylococci carried in the anterior nares and in non-bullous lesions seemed to resemble closely those causing infections in England, the bullous impetigo strains appeared to form a distinct group. Skin infectivity of the two types of staphyloccocus was therefore investigated.

The experiments were carried out in England during hot summer weather. The technique was as follows:

(1) The skin of the flexor surface of the forearm was washed thoroughly and dried with a clean towel. Scrubbing was avoided.

(2) A control culture was made by rubbing a circular area of about $^1/_2$ in.-diameter with a sterile wire loop moistened with nutrient broth. The culture was made on blood-agar.

(3) A "loopful" of an 18-hour broth culture of the test organism was applied to the area and allowed to dry in the open air.

(4) When the skin was dry a sterile plastic curtain ring of approximately $^3/_4$-in. diameter was placed over the area to maintain a space between the skin and the adhesive dressing which was applied finally. This dressing consisted of a piece of adhesive plaster approximately $1^1/_2$ in. square in the centre of which was cut a window about $^1/_2$ in. square. The window was closed by a sterile piece of cellophane, which allowed observation of the site.

The infectivity of a strain of *Staph. aureus* isolated from an impetigo bulla was tested on the skins of 12 subjects. The dressings were left undisturbed for 5 days, during which bullous lesions developed in 3 subjects but not in the remainder. In 2 instances the lesions were only about 1·5 mm. in diameter; but in the 3rd a bulla of 4 mm. diameter appeared—a size frequently observed in true bullous impetigo. It is perhaps significant that in each of the 3 subjects the lesions formed immediately beneath or adjacent to the curtain ring used in the dressing and never in the central area of skin. This suggests that pressure on the skin from the ring may have caused sufficient local trauma to initiate the infection.

A simultaneous comparison of the infectivity of a strain of *Staph. aureus* from bullous impetigo and one from a boil was made on the forearm of 1 subject. The technique differed from the above in that fresh organisms were applied to the skin daily until lesions developed. The impetigo staphylococcus gave rise to two bullæ, of which the larger had a diameter of 4 mm., while the organism from the boil produced only small papules which subsequently became pustular. When the experiment was repeated in much cooler weather, the boil staphylococcus gave rise to lesions similar to the previous ones, but the impetigo organism produced no lesions at all.

Although the scope of these experiments was limited, they suggest that some tropical strains of *Staph. aureus* may differ from their English counterparts in the type of skin lesion they produce. Possible differences in skin susceptibility to infection in the tropics and in England, perhaps induced by climatic differences, seem unlikely to provide the explanation.

Institute of Diseases of the Chest, London, S.W.3. J. R. MAY.

1. Foster, W. D., Hutt, M. S. R. *Lancet*, 1960, ii, 1373.
2. May, J. R. Tropical Bullous Impetigo. M.D. thesis, Cambridge University, 1951.

HÆMODIALYSIS AND CONTROLLED ULTRAFILTRATION

SIR,—We were interested in the paper by Dr. Twiss and Dr. Paulssen (Nov. 12) and in the letter by Mr. Ritchie and his colleagues (Dec. 10) about the ultrafiltrating properties of the Alwall artificial kidney and the Kolff twin-coil kidney respectively. Both groups of workers increased the rate of ultrafiltration by increasing the outflow pressure from the blood channels. The alternative of reducing the pressure in the dialysing fluid below atmospheric is preferable because the rate of blood-flow is not interfered with. This is of particular

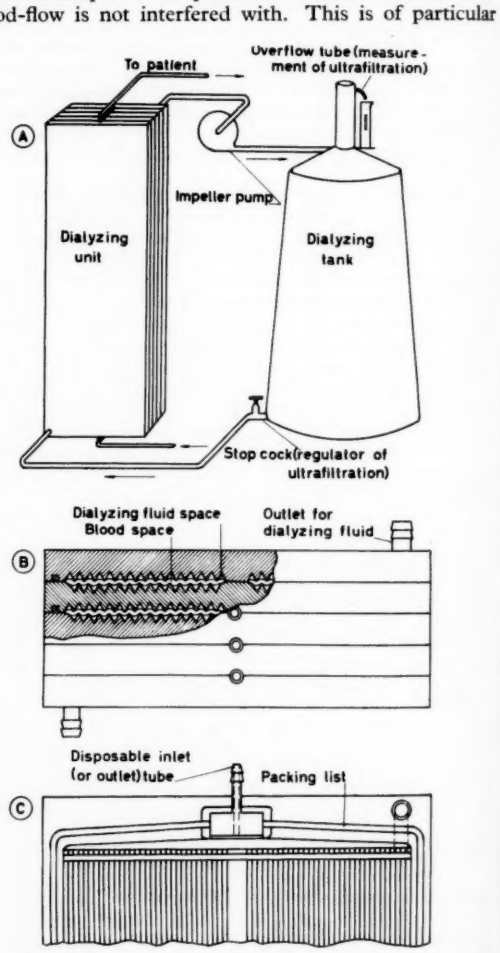

Fig. 1—(A) Parallel-flow four-channel hæmodialyser; (B) cross-section of dialysing unit; (C) end-section of plastic board used in dialysing unit.

importance in a low-resistance kidney when a blood-pump is not used.

This principle is used in a plastic parallel-flow artificial kidney recently constructed [1] (fig. 1). The pressure-drop in the blood channels between inlet and outlet tubes is 10 mm. Hg at a blood-flow of 300 ml. per minute. Dialysing fluid at a rate of 5 litres per minute is sucked through the kidney by an impeller pump and recirculates. After assembling the plastic boards which form the dialysing unit, a subatmospheric pressure of 50 mm. Hg is maintained in the dialysing channels by regulating the stopcock on the outflow tube from the dialysing tank (fig. 1A). In this way the membranes are stretched (fig. 1B) and the blood-space is easily filled. By further reducing the pressure any rates of ultrafiltration can be obtained up to and over 1 litre per hour when the pressure gradient over the membrane is 300 mm. Hg. Another advantage of subatmospheric pressure in the dialysing space rather than high pressure in the blood-circuit is that the boards are not driven apart. The expansion of the blood channels is more a function of the distance between the tops of the ridges (1·5 mm.), than of the distance between the boards, but is less than 40 ml. at working rates of ultrafiltration, even when the thinnest obtainable ' Cellophane ' membranes are used.

This volume-change and periodic volume fluctuations of less than 30 ml. in the thermostat-controlled dialysing tank, are the only volume-changes in an otherwise completely rigid system.

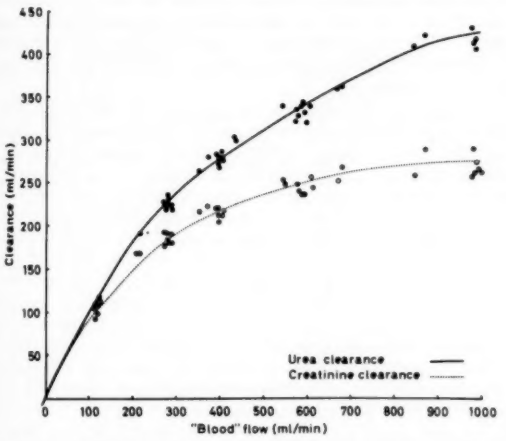

Fig. 2—In-vitro clearances at different perfusion-rates (membrane-area 2 sq. m.).

During ultrafiltration, when the volume of the dialysing system increases, the surplus flows through the overflow tube and is collected in a measuring cylinder (fig. 1A). In this way immediate measurements of rate of ultrafiltration are obtained. This measurement is more exact than that obtained even with the most sensitive bed weight.

Other virtues of this plastic parallel-flow hæmodialyser are:

(1) All parts in contact with blood are of polyethylene and polyvinyl and are disposable.

(2) It is easier to assemble than other parallel-flow kidneys, such as the Skeggs-Leonards type, because it consists of only five boards and no holes have to be made in the membranes before assembly. The problem of leakage is solved by rubber packing lists and moulded pieces against which the winged inflow and outflow tubes are pressed (fig. 1C).

(3) Urea and creatinine clearances are higher at all rates of blood-flow than in other models (fig. 2). This is due to improved distribution of blood. The cellophane-membrane area is approximately 2 sq. m., as against 1·8 sq. m. in an earlier model [1] with slightly lower clearances. The blood-volume of this kidney is 800 ml. By reducing the thickness of the blood-film by 0·1 mm. clearances just as high were obtained while the internal resistance of the kidney increased. Its low internal resistance is probably the main advantage in continuous hæmodialysis [2] without the use of blood-pump.

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F. KIIL
B. AMUNDSEN.

1. Kiil, F. *Acta chir. scand.* 1960, suppl. 253, 142.

A NEW THYROID PREPARATION

SIR,—Thyroid tablets, whether *B.P.* or *U.S.P.*, have been found to vary in potency from batch to batch and from manufacturer to manufacturer; but synthetic *l*-thyroxine sodium is uniformly effective though costing little more. Maclagan et al.[3] showed that the blood of healthy people contained 90% thyroxine and 10% triiodothyronine.

Since synthetic *l*-triiodothyronine sodium can also be obtained inexpensively, it seemed reasonable to combine the two substances in one pill in the same concentrations in which they appeared in normal blood. The full replacement dose of such a preparation is of the order of 0·3 mg. daily. Since triiodothyronine is rapidly effective and quickly excreted, a pill taken three times a day is better than one large dose.

This preparation has now been in use for about a year in all my patients requiring thyroid therapy, and seems to have definite advantages over traditional thyroid *B.P.* The patient notices an improvement as soon as medication is started and is thus encouraged to persist with treatment, whereas with thyroxine and thyroid tablets there is a lag of some days before appreciable improvement is noted.

A minority of patients have offered the information that they experience a sense of wellbeing when taking the tablets containing triiodothyronine which they had not noticed with thyroxine. Perhaps of more importance is that patients are often very quickly aware of having forgotten to take their tablets and so are less likely to default in this way.

Messrs. Glaxo kindly prepared and provided all the tablets, which are now marketed under the name of ' Diotroxin '.

King's College Hospital, London, S.E.5.

SELWYN TAYLOR.

B.C.G. VACCINATION AND TUBERCULOUS MENINGITIS

SIR,—B.C.G. vaccination, together with the improved standards of living and general hygienic conditions, antituberculous drugs, and screening-tests, undoubtedly plays an important role in decreasing the prevalence of tuberculous disease. Its role in the prevention and course of tuberculous meningitis in childhood is more debatable.

Our statistics on tuberculous meningitis demonstrate the advantages of B.C.G. vaccination. Fewer subjects vaccinated with B.C.G. develop tuberculous disease, and the overwhelming majority (subjects exposed to massive infection in their homes) are easily cured.

Instructions for vaccination were not always adhered to before 1952, and this may have influenced the statistics (see table). Since 1954, all our patients who fell ill despite previous vaccination have recovered.

	Recovered		*Died*	
Year	*Total*	*Vaccinated*	*Total*	*Vaccinated*
1947/48	8	–	72	1
1949	4	1	35	5
1950	6	2	27	3
1951	9	3	14	1
1952	12	3	6	1
1953	8	4	4	2
1954	3	–	4	–
1955	8	2	3	–
1956	7	2	3	–
1957	7	2	–	–
1958	5	1	1	–
1959	9	–	2	–

We have observed that, despite vaccination, a few cases of meningitis which cannot be relieved or influenced by treatment

2. Scribner, B. H., Caner, J. E. Z., Buri, R., Quinton, W. *Trans. Amer. Soc. artif. intern. Org.* 1960, 1.
3. Maclagan, N. F., Bowden, C. H., Wilkinson, J. H. *Biochem. J.* 1957, **67**, 5.

still occur; most of these are infants diagnosed too late or with very extensive spread of the disease.

The effectiveness of B.C.G. vaccination may differ from country to country, and generalisation from observations on one particular geographical area would therefore be rash.

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Hungary.

Z. ERDŐS
L. TURAI.

BRETYLIUM AND GUANETHIDINE

SIR,—Boura et al.[1] and now Professor Zaimis (Jan. 28) have suggested that acquired tolerance to bretylium may be due to the peripheral sensitisation of arterioles to the local effects of circulating catechol amines. One might, therefore, expect that drugs which act by blocking the peripheral effects of noradrenaline might prevent the development of tolerance or abolish it when present.

We have tried the effect of phenoxybenzamine hydrochloride (' Dibenyline ') in patients with acquired tolerance to bretylium. 6 patients with severe hypertension were studied; all had diastolic blood-pressures in the range 130 to 170, and 3 had had papilloedema in the past. They were receiving bretylium 1·8 to 3·4 g. daily, levels reached after progressive increases over 8 to 12 months' treatment. Phenoxybenzamine was added in a dose of 20 mg. daily, and increased by 10 mg. weekly. By the time a dose of 40–50 mg. had been reached, 5 patients had considerable falls in lying and standing blood-pressure, but all 6 were disabled by severe hypotensive symptoms on exertion, weakness, tiredness, and malaise. The dose of bretylium was then reduced by 0·6 g. daily, but in 5 cases even the standing blood-pressure was now uncontrolled, though exertional symptoms were still disabling. These 5 patients who had previously responded to less than 1·2 g. of bretylium daily now showed tolerance to a higher dose, even while receiving phenoxybenzamine 40–50 mg. daily in addition. In only 1 patient has the combination of the two drugs given acceptable control of blood-pressure without severe side-effects; and the study was, therefore, not extended over a wider series.

Such a small series does not enable any firm conclusions to be drawn but two suggestions seem warranted:

(1) The combination of bretylium and phenoxybenzamine does not seem likely to be clinically useful.

(2) Though these findings do not disprove, they do not give any support to the view that tolerance to bretylium is due to circulating noradrenaline acting on hypersensitive arterioles.

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R. D. LOWE.

SIR,—Professor Zaimis's letter of Jan. 28 warning against the use of excessive doses of bretylium and guanethidine deserves further support for probably more cogent reasons.

The possibility that tolerance to bretylium might result from increased peripheral sensitivity to adrenaline and noradrenaline was indicated in the first publication on the drug.[1] " Tolerance " apparently due to this cause was observed with large doses in cats, but there was little evidence of this during the first clinical examination in man. Further studies of " tolerance " in cats [2] showed that the increase in sensitivity of smooth muscles to circulating (injected or released) adrenaline and noradrenaline during daily administration of the drug, progressed to reach a maximum at two weeks. The change was comparable to that after postganglionic sympathetic-nerve section. Adrenergic nerves were still almost completely blocked even after continuing drug administration daily for six months.

1. Boura, A. L. A., Green, A. F., McCoubrey, A., Laurence, D. R., Moulton, R., Rosenheim, M. L. *Lancet*, 1959, ii, 17.
2. Green, A. F. *in* Adrenergic Mechanisms (edited by J. R. Vane); p. 148. London, 1960.

At first it seemed that " tolerance " to bretylium might be entirely explained by hypersensitivity to circulating pressor amines secreted mainly from the adrenal medulla, the activity of which is not depressed by bretylium. But more recently it was realised that the effects of the amines known to be released locally at adrenergic nerve-endings by bretylium might also be increased. Mr. Boura and I have now shown that this is so. Smooth muscle becomes greatly sensitised to this indirect contracting action of bretylium, during daily administration of the drug. We have found, moreover, that the changes during daily administration of guanethidine are similar.

We also confirmed that ganglion-blocking agents increase peripheral sensitivity to circulating adrenaline and noradrenaline, but that " tolerance " in cats is less extreme. This may be due to these agents not releasing amines directly but on the contrary depressing their secretion by the adrenal medulla. Also the increase in sensitivity to adrenaline and noradrenaline is not as great as that after bretylium or guanethidine.

Parallel observations with bretylium in man demonstrate that this drug not only blocks sympathetic innervation to cause a loss of peripheral vascular tone, but also has effects due apparently to adrenaline and/or noradrenaline release. These effects are normally so small with intravenous injection that they may be overlooked, but they have on occasion been reported.[3 4] That vasoconstrictor effects follow intra-arterial administration of bretylium is unquestionable.[1 5] Blair and his colleagues say: " The state of the vessels following an infusion of bretylium appears to depend on the balance between this constrictor action and the longer-acting sympathetic-blocking effect." [5] To explain tolerance we only have to suppose that the vasoconstrictor action progressively increases like the analogous effects in the cat.

Any increase of bretylium dosage above the amount needed to block the sympathetic innervation of blood-vessels is therefore likely, by causing further local adrenaline and/or noradrenaline release, to increase the tone of the blood-vessels and negate the advantage gained by sympathetic blockade. I would also suggest that this may explain why there are such extreme opinions on the clinical value of this drug. Despite some opinions to the contrary, Sir Horace Smirk [6] still considers bretylium to be a valuable drug for the treatment of many forms of hypertension. It seems significant that the dose-levels he uses are smaller than those of some other physicians, and that he believes in applying orthostatic hypotension to control of blood-pressure. Perhaps it is because he keeps the dose to a minimum that tolerance is apparently not a serious problem in his patients. He does not rely on the use of the one drug:[6 7] " In patients requiring large doses of bretylium tosylate, potent ganglionic-blocking agents such as pempidine, ' M & B 5409A ', ' M & B 4500 ', or mecamylamine, in appropriate doses, may be used to replace a proportion of the bretylium tosylate without causing parasympathetic side-effects." [7] The ganglion-blocking agents may reduce the adrenal-gland activity, and so lower the level of circulating adrenaline and noradrenaline. The likelihood of side-effects due to a preponderance of parasympathetic innervation after sympathetic blockade alone is also reduced. The background therapy recommended by Sir Horace includes reserpine.[6] In animals reserpine lowers the level of noradrenaline available to release by bretylium.

Complete " escape " from the hypotensive action of guanethidine may also be observed. A similar explanation to that offered for bretylium may well hold good. Guanethidine is known to cause noradrenaline release in animals and symptoms of this are found with intravenous dosage in man.[8] One possible factor for " tolerance " in man being less prominent with this drug than with bretylium, in the experience of some investigators, may perhaps be the practice of increasing the dose

3. Taylor, S. H., Donald, K. W. *Lancet*, 1960, ii, 389.
4. Conway, J. *Ann. N.Y. Acad. Sci.* 1960, **88**, 956.
5. Blair, D. A., Glover, W. E., Kidd, B. S. L., Roddie, I. C. *Brit. J. Pharmacol.* 1960, **15**, 466.
6. Smirk, F. H. *Practitioner*, 1960, **185**, 471.
7. Hodge, J. V., Smirk, F. H. *Amer. Heart J.* 1960, **60**, 539.
8. Richardson, D. W., Wyso, E. M. *Ann. N.Y. Acad. Sci.* 1960, **88**, 944.

very cautiously in case the resulting sympathetic blockade might be too great and too persistent.

The assumption is made above that there is probably a progressive increase in the sensitivity to adrenaline and noradrenaline during daily administration of bretylium and guanethidine in man as in cats, at a rate which may vary with the dosage of these drugs. Acute increases in sensitivity are known, but progressive increases have not yet been looked for (D. R. Laurence, personal communication).

Whether the increase in sensitivity of smooth muscle to noradrenaline and adrenaline caused by bretylium and guanethidine is independent of the blockade of adrenergic neurones, as Professor Zaimis suggests, is questionable. It could be a result of blockade of these neurones. In animals in which full adrenergic-nerve blockade is maintained, the increased sensitivity to the constrictor substances progresses during the first two weeks, like the increase after section of adrenergic nerves. Dr. Laurence told me that in man the increase in sensitivity to adrenaline and noradrenaline caused by a single dose of bretylium was not accompanied by a concomitant increase in sensitivity to hypertensin.

The Wellcome Research Laboratories, Beckenham, Kent. A. F. GREEN.

DERMATOLOGICAL APPOINTMENTS

SIR,—In your issue of Jan. 28 there are two advertisements for consultant dermatologists.

One is a joint appointment with the Manchester Regional Board and the United Manchester Hospitals for 8 sessions a week to include clinical duties at 8 hospitals with beds at 2. In addition, the holder " will be expected to spend an appropriate time in research . . . and will be eligible for consideration for a part-time University appointment ". This is presumably the senior teaching post in dermatology in Manchester. The other post is in Cumberland and North Westmorland and is whole-time or maximum part-time (9 sessions). The duties consist of clinical responsibilities at 3 hospitals, the care of a small unit of 14/16 beds at 1, and occasional beds at the other 2.

The contrast between the two posts in work involved is so great that one wonders how the authorities concerned arrived at their decisions. If the second post (Cumberland) is considered reasonable, then the first post (Manchester) entails so much work that not even a superman could do justice to the demands and responsibilities. And because an important part of the work is the organisation and teaching of dermatology to undergraduates and postgraduates it will not be surprising if even more medical students in the next generation complete their training saying: " Of course I know nothing about skins."

It is to be hoped that the authorities in Manchester will reconsider their advertisement, and amend it in accordance with a more realistic assessment of present-day needs.

Manchester. G. AUCKLAND Consultant Dermatologist.

HEADACHE AND PSEUDOXANTHOMA ELASTICUM

SIR,—I recently saw a man of 25 who had complained of " migraine " resistant to all forms of treatment. I was impressed by his mask-like expression and I noted a few accidental razor cuts on his loose cervical skin. Interestingly enough he stated that his mother also had loose skin around her neck. She, too, had complained of life-long headaches.

Closer inspection revealed other typical changes of pseudoxanthoma elasticum—i.e., retinal angioid streaks, diminished radial pulses, and slight hypertension (145/90 mm. Hg)—and skin biopsy from the neck, antecubital fossa, and abdomen confirmed the diagnosis of pseudoxanthoma elasticum. Von Kossa's stain showed heavy calcium deposition in the abdominal section but little in the other two specimens. Skin biopsy from the abdomen at the age of 14 had shown identical changes.

X-rays showed no intracranial or peripheral arterial calcification. There was no cranial bruit or neurological signs. The cerebrospinal fluid was normal. Full blood examination, electrophoretic strip, electrocardiogram, and chest X-ray were all normal. Stools were negative for occult blood, and a mid-stream specimen of urine was normal.

Typical changes can sometimes occur in the media of cerebral vessels (occasionally with aneurysmal dilatation). This could explain his headaches. Perhaps some of your readers have seen other cases presenting in this way.

Military Hospital, Delhi Barracks, Tidworth, Hants. D. P. MULLAN.

TREATMENT OF BEDSORES AND CHRONIC ULCERS WITH TOPICAL ASCORBIC ACID

SIR,—The healing of wounds is known to be impaired in patients with an inadequate intake of vitamin C (ascorbic acid), and Wolbach and Howe [1] showed that in scorbutic animals the fibrous tissue of recent wounds was deficient in collagen fibres.

Gould and Woessner [2] have clearly demonstrated that ascorbic acid is necessary for collagen formation. This means that ascorbic acid is essential for the production of connective tissue in the healing of wounds and in the maintenance of established scar tissue.[3] Noting that the rate and efficiency of primary wound healing depended to a great extent on vitamin C, Wolfer et al.[4] made these two points: (1) " When circumstances for healing are poor, such as the presence of undue wound tension or diminution of blood supply, this depletion [of ascorbic acid] is made more evident through gross failure of primary wound healing," and (2) " The incidence of wound infection under such circumstances suggests the need for ascorbic acid in the tissues for maximum resistance to infection by favouring primary wound healing ".

Chronic ulcers are usually associated with impaired blood-supply, and often associated with infection, so that it would seem reasonable to give large oral doses of vitamin C to provide the excess needed to overcome these factors. Unfortunately, this rarely meets with much success. A probable explanation is that the high serum level of ascorbic acid is ineffective because of local conditions. Gould and Woessner [2] suggested that the effect of ascorbic acid on collagen formation is a purely local one, and experimental studies by Gould [5] proved that ascorbic acid plays a vital and a local role in the formation of collagen. Gould also found that oral vitamin C had an additive effect. Accordingly, since the beginning of this year I have used local ascorbic acid in the treatment of pressure bedsores and chronic ulcers, particularly in bed-fast geriatric patients who usually have arteriosclerosis and often some concurrent low-grade infection.

Patients with indolent ulcers or pressure sores have been treated for at least 10–14 days by the usual methods: relief of pressure and control of incontinence were achieved when possible, and vasodilator and antibacterial therapy given when necessary. If at the end of this time no progress was noted I started topical ascorbic-acid therapy.

This consisted of irrigation of the ulcer with a sterile isotonic solution containing 15 mg. per ml. of ascorbic acid at pH 6, after which the wound was dressed with gauze soaked in 5 ml. of the same solution. This procedure was repeated daily for a week.

1. Wolbach, S. B., Howe, P. R. *Arch. Path.* 1926, **1**, 1.
2. Gould, B. S., Woessner, J. F. *J. biol. Chem.* 1957, **226**, 289.
3. Abt, A. F., Schuching, S. von, Roe, J. H. *J. Nutr.* 1960, **70**, 427.
4. Wolfer, J. A., Farmer, C. J., Carroll, W. W., Manshardt, D. O. *Surg. Gynec. Obstet.* 1947, **84**, 1.
5. Gould, B. S. *J. biol. Chem.* 1958, **232**, 637.

Twenty-two patients have now completed this course of treatment: three have shown little improvement, but in the remaining nineteen there has been a dramatic change with development of profuse fresh granulations. Many of these elderly patients had had extremely indolent ulcers that had shown no improvement for months and even years. It is therefore unlikely that the sudden change with the formation of granulation tissue could have been part of the natural course of the lesion.

Once these fresh granulations had formed after seven days' topical ascorbic treatment, the vitamin C was omitted and the wound left to heal spontaneously. In seventeen patients healing has been complete, and eleven have been discharged from hospital; the others, started more recently, are progressing satisfactorily.

Two more recent cases are showing steady improvement, but three patients with declining physical condition were not significantly altered by the " topical ascorbic acid treatment ".

The use of topical ascorbic acid in the treatment of indolent pressure sores is worth further investigations, both clinical and pathological.

I should like to thank the nursing staff for their unceasing efforts on behalf of their patients and John Wyeth and Brother, Limited, for supplying the ampoules of ascorbic acid solution at my request.

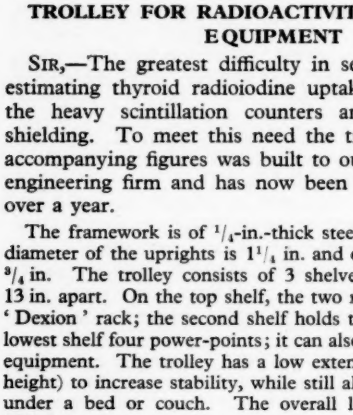
Geriatric Unit,
St. Alfege's Hospital, London, S.E.10. A. J. MESTER.

TROLLEY FOR RADIOACTIVITY MEASURING EQUIPMENT

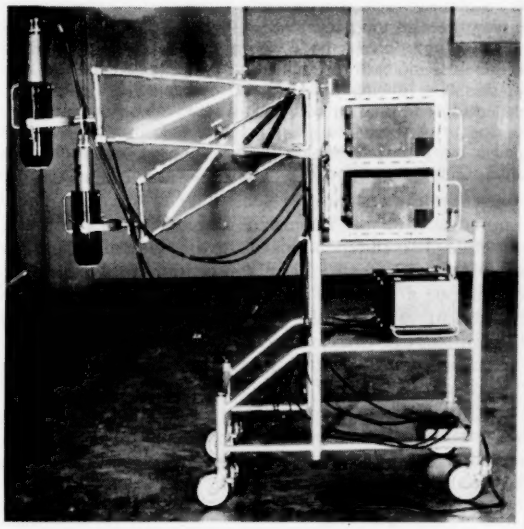
SIR,—The greatest difficulty in setting-up a unit for estimating thyroid radioiodine uptake is in suspending the heavy scintillation counters and their associated shielding. To meet this need the trolley shown in the accompanying figures was built to our design by a local engineering firm and has now been in constant use for over a year.

The framework is of $^1/_4$-in.-thick steel tubing; the internal diameter of the uprights is $1^1/_4$ in. and of the horizontal bars $^3/_4$ in. The trolley consists of 3 shelves, 21 in. square, and 13 in. apart. On the top shelf, the two ratemeters slide into a 'Dexion' rack; the second shelf holds the recorders, and the lowest shelf four power-points; it can also be used for ancillary equipment. The trolley has a low extended base ($10^1/_2$ in. in height) to increase stability, while still allowing the foot to go under a bed or couch. The overall length of the base is $37^1/_2$ in.

The scintillation heads are mounted on adjustable arms (E.R.D. Engineering Co., Ltd., Slough, Bucks) and the arms pivot on steel rods fitted into two hollow uprights. The steel rods project 21 in. above a fixed collar which prevents the rods moving further down the upright. The extent to which the arms can be raised is limited; to make more variations in height possible, steel spacing collars can be fitted on to the rods. The collar-sizes are 1, 2, 3 and 5 in., thus giving a wide range of heights.



The trolley is fitted with $5^1/_2$ in. castors (each with a foot-operated brake) (Homa Engineering Co., Ltd., Cosby, Leicestershire).



Compared with a mobile X-ray stand which carries only one scintillation detector and costs approximately £200, this trolley is easier to move, carries 2 scintillation detectors, and costs only about £50.

Department of Pathology,
Royal Infirmary,
Preston, Lancashire. G. R. A. PADMORE
F. RAMSDEN.

PHENYLKETONURIA IN JEWS

SIR,—Phenylketonuria has been thought to be particularly rare among Jews. We have been able to trace only one reference to this condition in a Jewish family.[1] On the other hand, there have been many references to its absence among Jews.[2–7] Among the general population of the United Kingdom and America the incidence of phenylketonuria has been estimated as 1 in 25,000 to 1 in 50,000 of the general population, while the incidence in institutions for mental defectives is 0·5–1·5%.[8–10]

About a year ago we came across two Yemenite Jewish families in Israel each of which had 2 defective children. Chromatographic examination of their urines, as well as their greatly raised serum-phenylalanine levels, proved them to be phenylketonurics. Later another case was found in an oriental Jewish family.

This led us to examine the urines of defective children in institutions. This work is still in progress, but so far about 1000 urines have been examined by Dr. S. Pollak, and 5 additional cases have been recognised. These children all belong to the oriental non-Ashkenazi group, and as this ethnic group forms some 60% of the material examined, the frequency among them appears to approximate to the 0·5–1·5% reported elsewhere. The rarity of phenylketonuria among Jews examined in Europe, England, and the United States refers probably to the Ashkenazi group who form the majority there and among whom no cases have been found in Israel either.

It is also of interest that most of our children have dark complexions, with dark and even black hair and deep-brown

1. Cohen, P., Kozin, P. J. *J. Pediat.* 1949, **34**, 76.
2. Centerwall, W. R. *J. Amer. dent. Ass.* 1960, **36**, 3.
3. Wright, S. W. *J. Amer. med. Ass.* 1957, **165**, 16, 2079.
4. Penrose, L. S. *in* Biology of Mental Defect; p. 142. New York, 1949.
5. Elliott, K. A. C., Page, I. H., Quastel, J. H. *in* Neuro-chemistry; p. 808. Springfield, Illinois, 1955.
6. Wright, S. W., Tarjan, G. *Amer. J. Dis. Child.* 1957, **93**, 405.
7. Kretchmer, N., Etzwiler, D. D. *Pediatrics*, 1958, **21**, 445.
8. Harris, H. *in* Human Biochemical Genetics; p. 36. London, 1959.
9. Jervis, G. A. *Ass. Res. nerv. ment. Dis. Proc.* 1954, **33**, 259.
10. Moncrieff, A. *Lancet*, 1960, ii, 273.

eyes, in contrast to the blondes with fair skin and blue eyes who are commonly said to form even up to 80% of cases.[11]

We are now investigating the genetic pattern and the biochemical disturbances in these children, as well as in their parents and siblings, to establish whether these aspects are identical with conditions reported in other races.

Pædiatric "B" Department,
and Biochemical Laboratory,
Tel Hashomer Government Hospital,
Israel.

BERNARD E. COHEN
EVA BODONYI
ARIEH SZEINBERG.

POMP AND CIRCUMSTANCE

SIR,—Professor Sanjivi (Feb. 4) has serious misgivings about the use of a teaching-room on the ward and fears that this may lead to more didactic teaching and less emphasis upon physical signs and clinical problems. I am sure that his anxiety, shared by many clinicians in this country, is due to a misunderstanding of the real purpose of the room. It should be used to amplify and supplement and never to replace bedside instruction.

Few teaching hospitals make special provision for ward teaching. Discussion necessarily takes place at the bedside, in the centre of the ward, in a sluice-room or empty side-ward, or in a draughty corridor with constant interruption. In previous communications [12 13] I set down the use that is made of the teaching-room in the gynæcological ward of the Royal Victoria Infirmary. Once the patient's history had been taken and any clinical signs demonstrated it is to the advantage of patient, teacher, and students that further discussion should take place away from the bedside. The patient is spared anxiety, teacher and students can speak freely. The room must be permanently set aside for teaching, and there are advantages in having a selection of visual aids readily available. A case of vulval leucoplakia may be demonstrated to students in the ward and then, from the collection of colour transparencies in the teaching-room, several other examples of the same condition may be shown. These colour transparencies can be compared with others showing early cancer of the vulva. In this way students can learn to appreciate more clearly the differences between benign leucoplakia and early cancer of the vulva. This use of the teaching-room gives added point to clinical teaching on the ward.

My experience over the past five years has shown that a ward teaching-room suitably equipped and properly used is capable of making a significant contribution to the clinical teaching programme.

Department of
Midwifery and Gynæcology,
Royal Victoria Infirmary,
Newcastle upon Tyne, 1.

J. K. RUSSELL.

POSITIONING FOR GALLBLADDER SURGERY

SIR,—Difficulty in operating on the gallbladder or bile-ducts is caused because these organs lie under the liver, and the liver itself lies under the rib-cage. Several manœuvres surmount this difficulty. The most radical of these is to open the chest, divide the diaphragm, and dislocate the liver into the chest, and is unwarrantable unless considerable difficulty is anticipated, as in some secondary operations on the hepatic ducts. Another method is to dislocate the liver partly out of the abdomen over the costal margin, but this cannot always be done because the parts lack mobility.

Formerly it was thought that better access to the biliary apparatus could be obtained by placing a cushion or rest under the lower dorsal spine, but this was not helpful in difficult cases, and often gave the patient severe backache. I have not found Kocher's incision advantageous.

After experimenting with these methods, and also with an incision through the bed of the 11th rib, I conclude that the most generally applicable and successful method is to twist the patient about his spinal axis so that the liver tends to fall to the right and the intestines to the left.

A table with a lateral tilt is helpful, as it can be easily adjusted. A sandbag is placed under the right buttock to lift it about 4 in. above the table-surface. The table is then tilted to the right until the lower abdominal surface is nearly horizontal. The abdomen is opened through a right upper paramedian incision. Assistance is required to retract the duodenum and other intestines to the left; but it is seldom necessary to retract the liver or costal margin.

I always use this method now and have done so for the last three years at the General Hospital, Birmingham.

Birmingham. FAUSET WELSH.

THE WRIGHT NEBULISER

SIR,—Those with experience of the Wright nebuliser will confirm the efficiency of this atomiser. One point has, however, been overlooked—namely, the instability of certain drugs on exposure to light. For example, isoprenaline spray changes colour within three days when stored in the nebuliser. If the parts of the nebuliser were coloured, that would effectively protect photosensitive drugs for reasonable periods and eliminate unnecessary wastage and loss of optimal activity of light-sensitive drugs.

Pharmaceutical Department,
Sully Hospital,
Sully, Glamorgan.

H. L. DANIELS.

Parliament

N.H.S. Charges and Contributions

On Feb. 1 Mr. ENOCH POWELL, the Minister of Health, made the following statement:

The net estimates of the National Health Service and the Health Departments for next financial year indicate an increase of 11% over those for this year. This follows upon an increase of over 8% this year and over 6% the year before. The total cost in the current financial year is about £867 million, of which £663 million will be met by the Exchequer.

The Government are determined to continue their policy of developing the health service and, in particular, to carry through a long-term programme of modernising our hospitals. These objects would be in danger if the cost of the service to the Exchequer were allowed to go on increasing at so high a rate. The Government have, therefore, decided that certain steps to reduce the net estimates are necessary.

The cost of a number of items for which charges are made has increased substantially since the charges were last fixed, and it is proposed to adjust them.

The charges for dentures will be increased by amounts ranging from 5*s*. to 15*s*. On the other hand, in order to put more emphasis on conservation, the charges for dental treatment will not be raised, and children and expectant and nursing mothers will be relieved in future of the present charges for dentures.

The charges for spectacles will be increased by 5*s*. a pair, with a higher charge for bifocal and multifocal lenses. However, it is proposed that children aged 10 or over shall no longer be charged for spectacle lenses in any type of National Health Service frame.

The maximum charge for amenity beds in hospitals in England and Wales will be doubled from March 1.

The cost of the pharmaceutical services this year will be about £92 million gross, £80 million net. Since the charge for pre-

11. Knox, E., Hsia, Y. Y. D. *Amer. J. Med.* 1957, **22**, 687.
12. Russell, J. K., Mustart, D., Duncan, C. J. *Lancet*, 1956, ii, 383.
13. Russell, J. K. *ibid.* 1958, ii, 444.

scriptions was fixed at 1*s.* an item in 1956, the average cost of an item has increased from 5*s.* 10*d.* to 7*s.* 4*d.* The Government are proposing to raise the prescription charge to 2*s.* per item from March 1. We believe that this measure is necessary, along with others already taken or in hand, to restrain the increase in the cost of the pharmaceutical services.

The Government have decided that from June 1 orange juice, cod-liver oil, and vitamin tablets under the Welfare Foods Scheme will be sold at prices which cover the cost.

The existing arrangements for refund of prescription and other charges will remain in force, and arrangements will be made through the National Assistance Board for the free issue of vitamin supplements.

The Government also propose to increase the N.H.S. contribution from the beginning of July next by 1*s.* a week for the employed man—10*d.* from the employee and 2*d.* from the employer—and by the appropriate amounts for other insurance groups. This will increase the yield from the contribution by about £49 million in a full year.

All these changes apply to Scotland, except that relating to amenity beds, for which in Scotland the charges are adjusted automatically.

The effect of all the measures will be to reduce the net health estimates by about £50 million in 1961-62 and about £65 million in a full year.

Mr. KENNETH ROBINSON: Is the Minister aware that the comprehensive list of charges which he has just announced represents, in our view, the biggest single assault on the whole principle underlying the National Health Service since it was conceived, and a very serious inroad into the whole Welfare State? Is he aware that the charges which he has announced are so comprehensive in their nature that he even tried to take credit for the one or two charges which he has not increased?

We take particular exception to the increase in the National Health Service contribution, which, of course, is a poll tax and falls most heavily on those less able to bear it. As for the prescription charge, does the Minister not recall that a committee advised him that his department would probably save money by abolishing the prescription charge altogether? Is he aware that we regard the charging for welfare foods at cost price as being a peculiarly mean step to take? The Minister once resigned from office. Does he not think that as the Minister responsible for a great service like the National Health Service he would have done better to return to the back benches rather than agree to these charges? Mr. POWELL: On the contrary, I should have been betraying my trust if I had agreed to an increase in the budgetary cost of this service, for it would inevitably have resulted in the development of the service itself having to be curtailed or limited if these steps had not been taken. The hon. Gentleman referred to the National Insurance contribution as a poll tax. It falls, of course, to be considered in the context of the whole economic position of the country, of the earnings of those who will pay it, and of the tax system as a whole, but the proportion of average earnings which will, in future, be collected by way of the stamp is not appreciably greater, in the nearest practicable comparison, than it was in 1948.

Medical Examination of Prisoners

ON the adjournment on Feb. 2 Mr. LEO ABSE reminded the House that when in 1883 the Home Secretary gave instructions that, where there was reason to believe that a defence of insanity was to be set up in a murder case, the mental condition of the accused should be examined before the trial, he did so to aid the defence and not so that the prosecution could obtain evidence for its benefit. Even this solicitude for the defence, however, was looked at with suspicion by the judges, and in 1904 they insisted that not only must all medical reports obtained by the detaining authorities be handed over to the defence, but that in no circumstances must the issue of insanity be raised by the prosecution. Yet today the Prison Commissioners, irrespective of whether or not it was the intention of the defence to raise the question of insanity, were insisting on the right of their prison medical officers to attempt to interrogate every and any man accused of murder, and then to send the reports so obtained to the Director of Public Prosecutions.

The test—certainly since the Homicide Act 1957—in deciding whether provocation was of such a character as to justify a reduction of the charge from murder to manslaughter, was whether such provocation would have prompted a hypothetical reasonable man to slay another. If prison medical officers—nearly all of whom, lamentably, lacked any psychiatric diploma—after repeated interrogation of a man in custody, handed over a report to the Director of Public Prosecutions indicating any sign of unbalance in the accused, he could find himself convicted of murder; whereas if such a report had not been provided to the prosecution he would rightly have received the punishment attracted to a conviction for manslaughter.

Mr. Abse urged the Home Secretary to get back to his predecessor's original intentions; namely, that a report should only be obtained if mental incapacity was to be raised by the defence. If the existing malpractices continued, we were in danger of verdicts of murder being given as a consequence of a clandestine investigation conducted in a prison cell between a doctor and a patient he had compulsorily acquired, and not as a result of evidence which would otherwise have been placed before an open court. The position now being adopted by the Prison Commissioners required their medical employees to be flagrantly in breach of the Hippocratic oath.

Mr. DAVID RENTON, under-secretary of State for the Home Department, said that for about 50 years it had been established practice that a person who was in prison awaiting trial on a charge of murder should receive a medical examination as to his physical and mental condition. This was desirable for two reasons. The defence might wish to raise a plea of "Not fit to plead", of insanity, of diminished responsibility, and would not be able to do so unless properly armed with recent and thorough medical evidence. If such evidence was made available, it should be placed in the hands of the court. The court itself, especially in a case in which it was suggested that the prisoner was not fit to plead, would have to use the same initiative in placing this issue before the jury, and it was therefore right that the court should have the medical report in its possession. Mr. Renton thought that where Mr. Abse possibly had reason to doubt the practice was when copies of the report reached the hands of the prosecution. It was made known to the Royal Commission that that might happen. The question of whether the prosecution should receive reports was naturally one which had engaged the attention of the Home Office and of the other authorities concerned. He agreed that the Prison Commissioners' medical officer's report was not the only report which could be obtained, but there had been many cases in which it was easily the most convenient way of obtaining an accurate up-to-date report on a prisoner's mental condition. The reports were not made in any sense for the purpose of cross-examination by the prosecution and should never be used for that purpose.

Diagnosis of Pneumoconiosis

ON Feb. 3 Mr. LESLIE SPRIGGS asked the Minister of Pensions to reconsider the procedure for the diagnosis of pneumoconiosis and to accept that in occupations such as coal-mining and pottery pulmonary disability without radiological signs should be accepted as an industrial disease after 10 years' work in the occupation. Dr. BARNETT STROSS, who seconded the motion, said that in the year ended June, 1957, 13,500 people in England and Wales put forward a claim. Roughly half of them were rejected on X-ray examination alone. Yet in many cases X-ray findings were minimal or even absent though gross emphysema, bronchial spasm, and bronchitis were present. Mr. HAROLD FINCH asked that men with

bronchitis and emphysema as well as pneumoconiosis should be classified as having pneumoconiosis and should be assessed on the extent of their disability.

Mr. BERNARD BRAINE, joint parliamentary secretary to the Ministry, said that the motion was in effect asking for the inclusion among industrial diseases of some diseases which, though undoubtedly prevalent among coalminers, were also widespread among the population as a whole. The Industrial Injuries Advisory Council were emphatic that it would be contrary to the intention of the Act if "other diseases were brought in, as it were, through the back door under the guise of pneumoconiosis". If we got away from clear-cut industrial causation, the present sharp boundary of industrial risk would become so blurred that the need for a scheme separate from ordinary National Insurance sickness provisions would disappear.

More research into the possibility of occupational causation was needed and, as the Minister had already announced, arrangements were being made to take a sample of the sickness records of individual persons so that an analysis could be made of the nature and extent of the incapacity for work by occupation and geographical location. This analysis would begin in the twelve months starting in June. It should provide research-workers with useful information on the distribution of illnesses. It might help to focus attention on aspects of the problem, especially those presented in the present debate, by providing factual information which at the moment was missing.

Spokesman for the Opposition

Mr. Kenneth Robinson has been appointed the chief spokesman of the Opposition on health matters in succession to Dr. Edith Summerskill, who has become a life peeress.

QUESTION TIME

Scottish Hospital Building Programme

In a written answer Mr. JOHN MACLAY announced that provisional selection of the major projects that should, if possible, be started during the next ten years had been agreed with the regional boards. In consultation with the committees of management the boards were now filling in the outlines of these large projects. Expenditure on hospital building in 1962–63, subject to the economic situation and the voting by Parliament of the necessary money, would rise to a provisional figure of £4,800,000.

N.H.S. Costs

The following table shows 1959–60 expenditure for Great Britain as a percentage of expenditure in 1950–51 after adjustment for the change in the Price Index of Consumers' Expenditure from 1950 to 1959:

	%
Gross cost of National Health Service (excluding local health authority services)	124
Gross cost of pharmaceutical prescriptions dispensed in the year	148

Pharmaceutical Services

The gross cost of the pharmaceutical services in Great Britain is about £92 million in the current year, compared with £50¾ million in 1951–52. It is about 9% more than in 1959–60. It represents about 10½% of the estimated total cost in the current financial year of the National Health Service and the health departments.

The total sums refunded in respect of prescription charges were about £1,030,000 in 1959 and about £1,100,000 in 1960, representing about 20,600,000 and 22,000,000 prescriptions respectively.

Dentures and Spectacles for Children and Nursing Mothers

The estimated cost in a full year of removing existing charges for dentures for children, expectant mothers, and nursing mothers, and for spectacle lenses for children aged 10 years and over is £100,000 and £170,000, respectively, for Great Britain.

Pilkington Awards

Payment instructions for the retrospective payments due to medical staff under the recent salary award were issued on Jan. 12. Hospital authorities have been asked to make every effort to make payment by the end of March to doctors whose current addresses are known to them.

Obituary

ERIC CHRISTIAN GILLES

O.B.E., Dr.P.H. Harvard, D.Sc. Maryland, L.R.C.P.E.

Dr. Gilles, who died on Jan. 23 of a heart attack while investigating an outbreak of cerebrospinal meningitis in Kano Province, Northern Nigeria, was an able administrator and an outstanding practical health officer.

After qualifying in 1924 he served as port health officer in Colombo, before he moved to Nigeria in 1937 at the invitation of Sir Rupert Briercliffe, who had lately left Ceylon to become D.M.S. in Nigeria. Gilles served in Ibadan and Lagos before he was posted to Kano as medical officer of health. There he spent the war years, happily building up the environmental health services, and forming a lasting affection for "the walled city" and its people. During this period he published a number of papers on the disposal of town refuse by composting and other health subjects.

In 1945 he was promoted senior health officer, Northern Province, and moved to Kaduna, where he was soon caught up in the constitutional changes which started Nigeria on the road to independence. From a sleepy backwater, the Northern Province became an autonomous region within the Federation of Nigeria with its own Government and its own independent medical service, of which in 1952 Gilles became the first director. At first the service existed in little else but name, and its early years were a struggle against shortages of every kind. Under his leadership, however, things slowly improved, and when he retired, early in 1955, he was able to hand over to his successor a going concern.

On his retirement he was immediately appointed to succeed Dr. W. E. S. Merrett as principal of the Kano Medical School which was founded, largely on his own advocacy, to train Northern Nigerians as assistant medical officers, and thus help to stop the gap until there were enough fully qualified Northern Nigerian doctors to staff the service. Here too he had to contend with frustrating shortages, and it was with justifiable triumph that he saw the first four students graduate from the school last December. Soon afterwards he retired for the second time to live in the house which he had built for himself in Kano, tending his garden and his beloved roses, and working temporarily as medical officer of health.

A colleague writes:

"Gilles was not universally popular—directors of medical services seldom are—but to those who worked closely with him he was a loyal and generous chief, who inspired liking and respect. Despite what often seemed a rough approach, he had an intuitive insight into the mind of Nigerians, and a real sympathy for their aspirations which won him many Nigerian friends; and the O.B.E. awarded to him a few weeks ago was widely welcomed in Nigeria, as elsewhere."

Dr. Gilles leaves a widow, but no children.

KEITH STEWART THOMPSON
M.R.C.S.

Dr. Thompson, consultant pathologist to Selly Oak hospital group, died in Queen Elizabeth Hospital, Birmingham, on Feb. 1.

He qualified in 1930 from the London Hospital and, after holding a post as pathological assistant there, he became lecturer in the department of pathology in the University of Birmingham and pathologist to Queen's Hospital, later taking up his present appointment.

F. L. K. writes:

" Dr. Keith Thompson was essentially an enthusiast, who once he had made up his mind to do something, be it in connection with his work or his hobbies, tackled the problem with vigour and was not content until he had achieved his aim. He loved to talk and discuss all manner of subjects and had the power of convincing audiences of the correctness of his views by his lucid expositions.

" In the last three years he had given most of his time to the problems of hospital cross-infection, both the physical conditions in the wards themselves and the disinfection and sterilisation of all kinds of hospital equipment. His investigations into materials and their part in carrying infection involved the study of manufacturing and laundry processes, and his advice on modes of sterilisation was often sought. The more he observed these things the more did he drive himself to find the solution he wanted, and he did not spare himself in the effort. In many ways a most modest and self-effacing man, Dr. Thompson did not allow his name to appear among the titles of the film on cross-infection made in the Selly Oak group of hospitals, though he wrote the script and was the principal performer. As a Home Office pathologist he combined exceptional skill and tact in presenting the medical aspects of many personal tragedies with understanding and sympathy for the relatives.

" Off duty he was a genial companion and a great lover of the country life. He was never happier than when he was climbing in Snowdonia. A keen photographer of no mean merit and a lover of good music, he would always welcome his friends to his home and entertain them with examples of his hobbies and his lively conversation ".

Dr. Thompson leaves a widow, a son, and a daughter.

Sir GEOFFREY JEFFERSON

F. R. F. writes:

" It is thirty-six years since I first had the opportunity to marvel at the gifts of Geoffrey Jefferson—his outstanding distinction, his clinical judgment, his wide knowledge of people, well and ill, and his ability to think deeply about almost any subject. Many will not know of the uphill battle he had in the 'twenties and 'thirties to get a place in which to sit and think, a bed in which to put a patient, or a theatre in which to operate. In the later years, too, I used to feel that it was wrong if I saw him physically exhausted after a long operating session, when it seemed wiser that he should have been sitting in a congenial environment—pondering and reflecting—for one wanted to see so much the fruits of his labours.

" It is indeed sad to know that we will never hear again that merry chuckle or see that waistcoat ripple which accompanied the few words or the sentence which so ably and so wittily summarised or caricatured the whole situation—be it a clinical problem, one in committee, or in any discussion. On the other hand, let us be grateful that we have known him for so long and let us pay homage to one of the greatest medical thinkers of this century."

Births, Marriages, Deaths

DEATHS

BRAILSFORD.—On Jan. 28, at Queen Elizabeth Hospital, Birmingham, after a short illness Dr. James Brailsford of 20, Highfield Road, Edgbaston, Birmingham, 15.

Notes and News

GENERAL PRACTICE IN SCOTLAND

AT June 30, 1960, the Scottish Medical Practices Committee reports, there were 2638 general practitioners in Scotland (including 1801 practising in partnership) compared with 2614 (1753) in 1959. The average number of patients on doctors' lists was 1977 compared with 1988 in 1959. During the year 1959–60 23 vacancies were filled after advertisement, and 32 without advertisement; 40 vacancies were not filled and patients were transferred to other lists. One exchange of practice was arranged between an Aberdeenshire doctor and a Somerset doctor.

CASUALTY DEPARTMENTS

THOSE who would improve the service given to patients in casualty departments will be interested in two articles by Clarkson,[1] who examines the subject as it affects one of the London teaching hospitals. In the first article he discusses the function of the department, the source of the patients, the variety of medical work, and the accommodation and staff needed to carry it out. The second article describes—perhaps celebrates—the devotion of the whole of the ground floor of a modern surgical wing to this heterogeneous collection of clinical problems. Clarkson says that the casualty department, even in the largest hospitals, should act as receiving-room for " acute sick ", as well as for accident cases; and it is in this department (not at the " hospital door ") that segregation should first take place. He declares, too, that definitive treatment of ambulant patients should be carried out in the casualty department, which should maintain a fracture clinic. A certain amount—admittedly as little as possible—of " general practice " work is desirable, and indeed inevitable. The availability of valuable teaching material, as well as the intention to maintain a high standard of treatment, call for the frequent attendance of a consultant in the department. (A case analysis shows that 11% of first attendances were seen by a consultant.)

The second article, on the accommodation shortly to be offered to this casualty staff when the new wing is opened, must fill the average casualty surgeon with envy if he compares this with his own.

University of Cambridge

On Jan. 28 the following degrees were conferred:

M.B., B.Chir.—* P. F. Bates.
M.B.—D. R. Bainbridge, * Chin Cheung Chan, * Hung Cheng, * Marjorie C. Doddridge, * Kenneth Lumsden, Jane M. Robson, * J. H. Thormley, F. W. Webb, E. D. G. Williams.
* By proxy.

University of London

The title of Sir William Collins professor of anatomy in the university has been conferred on Prof. G. W. Causey, in respect of his post at the Institute of Basic Medical Sciences.

Prof. Causey, who is 53 years of age, was educated at Wigan Grammar School and the University of Liverpool. He graduated M.B. with first-class honours in 1930 and gained the F.R.C.S. three years later. After holding a surgical registrarship at the Liverpool Royal Infirmary and serving as an assistant-surgeon at Walton Hospital he came to London to take up a lectureship in anatomy at University College. He was appointed to his present chair at the Royal College of Surgeons of England in 1952. His published work includes papers on the peripheral nervous system and electron microscopy.

The title of reader in anatomy has been conferred on Dr. A. S. Breathnach, in respect of his post at St. Mary's Hospital Medical School, and of reader in clinical rheology on Dr. D. G. Melrose in respect of his post at the Postgraduate Medical School of London.

University of Birmingham

The Ford Foundation has made a grant of $440,000 to support research in the department of anatomy into the reproductive physiology of monkeys.

1. Clarkson, P. *Guy's Hosp. Gaz.* Nov. 5 and Nov. 19, 1960.

University of Sheffield

A conference on accidents and rehabilitation for industrial medical officers, organised by the department of preventive medicine and public health, is to be held on April 15. Further particulars may be had from Prof. J. Knowelden, department of preventive medicine and public health, The University, Sheffield, 10.

University of Glasgow

Prof. C. M. Fleming has been appointed representative of the University on the General Medical Council for five years from Feb. 1, 1961.

The following appointments have been made:

Dr. S. Bhandarkar, research assistant in medicine, Western Infirmary; Dr. D. H. A. Boyd, lecturer in materia medica; Dr. David Charles, lecturer in gynæcological pathology; Mr. Robert Shields, lecturer in surgery, Western Infirmary.

University of Wales

Dr. J. D. Lever has been appointed to the chair of anatomy in the University College of South Wales and Monmouthshire in succession to the late Prof. J. S. Baxter.

Dr. Lever who is 37 years of age was educated at Westminster School, the University of Cambridge, and St. Thomas's Hospital. After qualifying in 1946 he held house-appointments at Charing Cross Hospital, and later served as a surgeon lieutenant R.N.V.R. In 1950 he went to Cambridge as an assistant lecturer in anatomy and five years later became lecturer. He proceeded to the degree of M.D. in 1954, and was elected to a fellowship of Trinity College, Cambridge, in 1957. His published work on functional morphology in the endocrine glands includes papers on the adrenal gland and diabetic pancreas and an electron microscopic investigation of the carotid body.

Royal College of Physicians of London

Prof. E. P. Sharpey-Schafer will deliver the Oliver-Sharpey lectures on March 7 and 9 at 5 P.M., at the college, Pall Mall East, S.W.1. His subject will be venous tone.

World Health Day

The theme chosen for World Health Day for 1961 is Accidents and their Prevention. It will be held as usual on April 7.

Medical War Relief Fund

During 1959–60 £475 was awarded in gifts, including three educational grants and four maintenance grants. Most of the educational commitments of the Fund are now complete, and two of the students intend to study medicine.

N.H.S. Committee on Health Education

The joint committee of the English and Scottish Health Services Councils on Health Education, of which Lord Cohen of Birkenhead is chairman, is now ready to receive written evidence. This should be submitted by May 31 to one of the joint secretaries: Mr. W. N. Judd, D.F.C. (Ministry of Health, Savile Row, London, W.1), and Mr. A. W. Tait (Department of Health for Scotland, St. Andrew's House, Edinburgh, 1).

Nutrition Society

On Saturday, March 18, at 10.30 A.M., at the London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1, this society is to hold a symposium on the place of food science and technology in the campaign against malnutrition. Further particulars may be had from the hon. programmes secretary of the society, Miss D. F. Hollingsworth, c/o Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, London, S.W.1.

National Association for Mental Health

This year the theme of this association's annual conference, which is to be held on March 9 and 10 at Church House, Westminster, London, S.W.1, is Mental Health is Everybody's Business. The conference is to be opened by Mr. Enoch Powell, the Minister of Health, and the speakers will include Prof. A. V. Neale, Dr. W. W. Sargant, Dr. Stanley Smith, Dr. W. A. Heaton-Ward, Prof. R. M. Titmuss, Dr. P. A. Tyser, and Dr. J. P. Horder.

Institute of Urology

A weekend course on medical aspects of renal diseases will be held at the institute, 10, Henrietta Street, London, W.C.2, from March 3 to 5. Further particulars will be found in our advertisement columns.

Research Trust for Royal Free Hospital

Mr. Peter Samuel, chairman of the Board of Governors of the Royal Free Hospital, London, has given £100,000 to form a research trust for the hospital and medical school. The five trustees are to be Mr. Samuel and his wife, and, ex officio, the dean of the medical school and the chairmen of the medical and finance committees.

Medical Legacies

The trustees of the estate of Mr. Alexander Edwards of Forres have allocated £122,000 to the following Scottish hospitals: Princess Louise's Scottish Hospital for Limbless Sailors and Soldiers, Erskine, Renfrewshire, £25,000; Stobhill General Hospital (pædiatric unit) Glasgow, £30,000; Forres Hospital, £15,000; Peterhead Hospital (new maternity unit), £15,000; Turner Hospital, Elgin, Morayshire, £26,000. This is in addition to the £80,000 already given to hospitals after the death of Mr. Edwards' widow three years ago.

Prof. Thomas Moorhead left half of the residue of his total estate of £110,000 to Trinity College, Dublin, to form the Mai Beatrice Moorhead memorial fund for some purpose connected with Dublin University, preferably in connection with the Medical School.

Mr. Bertie Lees Read, clerk to the governors of Guy's Hospital, left £2000 to the Institute of Hospital Administrators to provide a scholarship in hospital administration, and £5000 to the Board of Governors of Guy's Hospital for hospital purposes.

Commercial Development of Interferon

In the annual report of the National Research Development Corporation for 1959–60 (H.M. Stationery Office, 1*s.* 6*d.*) it is stated that the Corporation is cooperating with the Medical Research Council and firms in the United Kingdom pharmaceutical industry (Glaxo Ltd., Wellcome Foundation Ltd., I.C.I. Ltd.) to secure the development of interferon and to arrange for its commercial exploitation. These plans provide for the Corporation and the industrial firms to be shareholders in the G.N.R.D. Patent Holdings Ltd., which will handle the business arrangements.

Limitation of Claims in Cases of Injury

The Lord Chancellor and the Secretary of State for Scotland have appointed a committee to advise them whether legislation is desirable to amend the law relating to the limitation of actions in cases of personal injury where the injury or disease giving rise to the claim has not become apparent in sufficient time to enable proceedings to be begun within three years from the inception of such injury or disease. The chairman will be Mr. Justice Edmund Davies, and the medical members will be Sir Charles Dodds and Dr. Andrew Meiklejohn. Communications may be addressed to Mr. A. D. M. Oulton at the Lord Chancellor's Office, House of Lords, London, S.W.1.

Dangerous Fireworks

At Booth Hall Children's Hospital near Manchester there is a regional centre for the treatment of severe burns and scalds. Each year about Nov. 5 grave casualties are caused by fireworks; and on Guy Fawkes Day last year 11 seriously burned children were admitted, some of whom are still receiving treatment. The management committee of the hospital have sent a letter to the Ministry of Health, the Home Office, and the local Member of Parliament drawing attention to the injuries caused each year by fireworks, and saying that in their view it would be useless merely to prohibit the sale of fireworks to children. They believe that the only satisfactory course "would be to have properly controlled displays, perhaps under the supervision of the Fire Brigades".

International Congress of Allergology

This congress will be held from Oct. 15 to 20 in New York. Further particulars may be had from Dr. William B. Sherman, 60, East 58th Street, New York, 22.

International Cardiovascular Society

This society is to hold a congress from Sept. 7 to 9 in Dublin. Further particulars may be had from the secretary-general of the society, Dr. Henry Haimovici, 715, Park Avenue, New York, 21.

International Congress of Food Science and Technology

This congress will be held from Sept. 18 to 21, 1962, in London. Further particulars may be had from the hon. secretary of the congress, 14, Belgrave Square, S.W.1.

The British Postgraduate Medical Federation lecture on the scientific basis of medicine for Thursday, Feb. 16, has been postponed until Tuesday, March 7, owing to the visit of the Queen Mother to the London School of Hygiene and Tropical Medicine on Feb. 16.

The *Excerpta Medica* Foundation has appointed Mr. John Davis as manager of their new office in London, at 67, New Bond Street, W.1.

The Ministry of Health's *Hospital Building Note* No. 7 deals with accommodation for nursing staff. Copies (1*s.* 6*d.*) may be had from H.M. Stationery Office.

The Greater London Red Cross Blood Transfusion Service has moved to 4, St. Andrews Place, N.W.1. The new telephone numbers are Hunter 2579 and 3120.

CORRIGENDUM: *Treatment of Nasal Carriers of Staphylococci.*—In the letter by Dr. A. E. Gremeaux (Feb. 4, p. 284) we mis-spelt the proprietary names ' Tyrothricin ' and ' Soframycin '.

Diary of the Week

FEB. 12 TO 18

Monday, 13th

UNIVERSITY OF LONDON
5 P.M. (University College Hospital Medical School, University Street, W.C.1.) Dr. Arpad Csapo (New York): Nature Experiments on the Maintenance of Pregnancy.

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Emotional Reactions to Physical Illness.

Tuesday, 14th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
4 P.M. Sir Russell Brock: Museum, Research, and the Inspiration of Hunter. (Hunterian oration.)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.15 P.M. *Psychiatry.* Prof. Eugene Popov: Soviet Psychiatry.
5.30 P.M. *Experimental Medicine and Therapeutics.* Prof. A. D. M. Greenfield, Dr. R. F. Mottram: Human Forearm as an Experimental Preparation.

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. R. A. McCance: Control of Acid-base Stability in the Newly Born.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright-Fleming Institute.) Mr. J. A. Chalmers: Vacuum Extractor.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Mr. I. R. McCaul: Basal Ganglia Surgery.

MANCHESTER MEDICAL SOCIETY
8 P.M. (Clinical Sciences Building, York Place.) *Surgery.* Mr. H. B. Torrance, Mr. A. G. Riddell, Mr. A. R. Anscombe: Surgery of the Liver and its Circulation.

Wednesday, 15th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. A. A. Sharp: Defibrination Syndrome.

ROYAL SOCIETY OF MEDICINE
8.15 P.M. *General Practice.* Dr. Margaret Dudley-Brown, Dr. H. G. Farquhar, Dr. Ronald Mac Keith: Early Diagnosis of Congenital Abnormalities.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. G. C. Wells: Histochemistry of the Dermis.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. E. H. Hudson: Cysts of the Lung.

HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W.1
8.15 P.M. Prof. P. M. Daniel, Dr. R. W. Riddell, Dr. Raymond Hierons: Clinicopathological meeting.

Thursday, 16th

ROYAL SOCIETY OF MEDICINE
3.45 P.M. *Dermatology.* Dr. Hugh Gordon, Prof. J. D. Boyd, Dr. Henry Haber, Miss Phyllis George, Mr. A. K. Monro, Mr. C. F. Noon, Dr. Manuel Lederman: Symposium on Malignant Melanoma.
8 P.M. *Neurology.* Sir Russell Brain: Neurology of Language. (Hughlings Jackson lecture).

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Dr. N. F. C. Gowing: Role of the Pathologist and Management of Laryngeal and other Neoplasms.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W.1
7.30 P.M. Prof. W. St. C. Symmers, Dr. Ian Murray, Dr. Mary Marples: Fungus Diseases.

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W.1
8 P.M. Mr. B. B. Milstein, Dr. D. A. W. Edwards, Dr. F. R. Berridge: Mechanism of the Cardia.

NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Orthopædic Hospital, Oxford
8.30 P.M. Dr. W. M. Rigal: Chondrogenesis.

MANCHESTER MEDICAL SOCIETY
8 P.M. (Staff House, University of Manchester.) *Anæsthetics.* Dr. Joseph Greenan: Cardio-œsophageal Junction. Dr. J. B. Montgomery: Emergency Obstetrical Anæsthesia.

UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology department, Queen's College, Dundee.) Prof. D. D. Reid: Ætiology of Bronchitis.

Friday, 17th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Dr. H. B. G. Robinson (University of Kansas): Effects of Operative Procedures upon the Dental Pulp. (Webb-Johnson lecture.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. Rodney Smith: Anatomical and Physiological Considerations in Hepatic Resection.
4 P.M. Prof. J. W. Crofton: Sarcoidosis.

ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Epidemiology and Preventive Medicine.* Dr. James Grant, Dr. E. L. Feinmann, Dr. K. M. Martischnig: Study of Control Methods in Tuberculosis.

FACULTY OF RADIOLOGISTS
4.30 P.M. (Royal College of Surgeons of England.) *Radiodiagnosis section.* Dr. Louis Kreel: Nephrocalcinosis. Dr. G. H. Moss: Intermittent Sigmoid Volvulus. Dr. R. G. Pitman, Dr. R. E. Steiner, Dr. Z. L. Szur: Radiological Appearances of the Chest in Polycythæmia Vera.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
3.30 P.M. Mr. William McKenzie: Management of Chronic Suppurative Otitis Media.

BRITISH TUBERCULOSIS ASSOCIATION
5 P.M. (26, Portland Place, W.1.) Dr. E. J. Moran Campbell, Dr. Philip Hugh-Jones, Dr. F. Harwood Stevenson, Dr. M. K. Sykes, Dr. T. M. Wilson: Assisted Respiration.

ROYAL COLLEGE OF SURGEONS OF EDINBURGH, Nicolson Street, Edinburgh, 8
3.30 P.M. Mr. Arthur Jacobs: Reconstructive Surgery of the Urinary Tract.

Saturday, 18th

MCGIBBON LECTURE
2.30 P.M. (Royal College of Physicians of Edinburgh, Queen Street, Edinburgh, 2.) Dr. A. Rae Gilchrist: Radiological Contributions to Cardiology.

Appointments

BACON, A. P. C., M.B. Cantab., M.R.C.P.: part-time consultant in general medicine and Geriatrics, Scarborough Hospital.

CONDON, H. A., F.F.A. R.C.S., D.A.: part-time consultant anæsthetist, Royal National Throat, Nose, and Ear Hospital, London.

JONES, A. G., M.A. Oxon., M.R.C.O.G.: assistant S.H.M.O., duties include planning, organisation, and staffing of the hospital and specialist services, Oxford Regional Hospital Board.

MACNAMARA, JAMES, M.D. N.U.I., M.R.C.P.: chest physician (S.H.M.O.), Royal Victoria and Northern hospital group, Edinburgh.

PARSONS, H. M., F.R.C.S., D.L.O.: assistant director, audiology unit, Royal National Throat, Nose, and Ear Hospital, London.

TIBBS, D. J., M.C., M.B. Lond., F.R.C.S.: consultant surgeon, United Oxford Hospitals.

Birmingham Regional Hospital Board:

BROWNE, R. A., M.B. N.U.I., D.P.M.: consultant psychiatrist and medical superintendent, Coleshill Hall Hospital.

CLARKE, GORDON, M.B. Manc., F.F.A. R.C.S., D.A.: part-time consultant anæsthetist, Stoke-on-Trent hospital group.

DAVIES, W. H., M.CHIR. Cantab., F.R.C.S.: part-time consultant surgeon, Herefordshire hospital group.

GOULDEN, W., M.R.C.S.: assistant psychiatrist, Monyhull Hospital, Birmingham.

MCQUILLAN, JOHN, M.B. Dubl., D.P.M.: consultant psychiatrist and medical superintendent, Burghill and Holme Lacy Hospitals, Hereford.

Leeds Regional Hospital Board:

DOWNSBROUGH, F. K., M.B. Leeds, D.M.R.D.: consultant in radiology, Bradford/Otley district.

LAMBERTY, N. A., M.B. Edin., M.R.C.P.E.: consultant in venereal diseases, York/Harrogate area.

MACKINNON, DONALD, M.D. Lond.: consultant in pathology, York.

RUSTAGE, J. H., M.B. Lpool, D.M.R.D.: consultant in radiology, Halifax/Huddersfield district.

TAINSH, J. M., M.B. Edin.: S.H.M.O. in infectious diseases, Seacroft Hospital, Leeds.

The Hospital for Sick Children, Great Ormond Street, London:

FIELD, PAUL, M.B. Lond., F.R.C.S.: registrar in thoracic surgery.

FROST, PHILLIDA M., M.B. Lond., F.F.A. R.C.S., D.A.: resident anæsthetic registrar.

STEPHEN, JOYCE M., M.B. Lond., D.P.M.: part-time M.O., department of psychological medicine.